Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Bleomycin PFI

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains Bleomycin sulphate, equivalent to bleomycin 15 units (USP) or 15 000 I.U.

One unit (USP) equivalent to 1 000 I.U. is equivalent to the biological activity of 1 mg.

Note: 1 mg active substance is determined by bioassay and is not identical to 1 mg dry substance.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to yellowish white powder for solution for infusion, injection or instillation.

Warning:

It is recommended that **bleomycin** be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available. Pulmonary fibrosis is the most severe toxicity associated with **bleomycin**. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Its occurrence is higher in elderly patients and those receiving greater than 400 units total dose, but pulmonary toxicity has been observed in young patients and those treated with low doses.

A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills and wheezing has been reported in approximately 1% of lymphoma patients treated with **bleomycin**.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bleomycin is useful in the management of the following neoplasms:

1) Squamous cell carcinoma affecting the mouth, nasopharynx and paranasal sinuses, larynx, esophagus, cervix, vagina, penis and skin. Well-differentiated tumors usually respond better than anaplastic ones.
2) Hodgkin's disease and other malignant lymphomas, including mycosis fungoides.
3) Testicular carcinoma (seminoma and non-seminoma).
4) Malignant effusions of serous cavities (intrapleural and intraperitoneal)
5) Additional indications in which **bleomycin** has been shown to be of some value include metastatic malignant melanoma, carcinoma of the thyroid, lung and bladder.

Local treatment of refractory warts. **Bleomycin** can be used as a single agent, but is generally used in combination with other cytotoxics and/or with radiation therapy.

4.2 Posology and method of administration

Bleomycin is administered parenterally by intramuscular injection, intravenous injection/infusion, intraarterial injection/infusion, subcutaneous injection, intratumoral injection or intracavitary instillation.

Posology

Adults

1) Squamous cell carcinoma

Intramuscular or intravenous injection of 10-15 units (USP)/m². Intravenous infusion of 10-15 units (USP)/m²/day over 6-24 hours for 4 to 7 consecutive days at intervals of 3-4 weeks.

2) Hodgkin's lymphoma and non-Hodgkin's lymphoma

Intramuscular or intravenous injection of 5-10 units (USP)/m² once or twice a week. Due to the possibility of anaphylactoid reactions, in lymphoma patients the first two doses should not exceed 1–2 units. If no acute reactions occur, the regular dosage regimen can be administered.

3) Testicular carcinoma

Intramuscular or intravenous injection of 10-15 units (USP)/m² BSA once or twice per week.

The dose of 15–20 units (USP)/m^2 BSA/day is administered by intravenous infusion over 6–24 hours on 5–6 consecutive days at intervals of 3–4 weeks.

4) Malignant effusions

60 units (USP) in 100 ml physiological saline intrapleurally or intraperitoneally as a single dose and repeated, if necessary.

5) Refractory warts

Intralesionally injection of **bleomycin** has been given as a 0.1 % solution, usually as a 0.1 ml injection.

In cases of Hodgkin's disease and testicular cancer, improvement occurs rapidly and may be observed within two weeks. If no improvement is noted by this point, subsequent improvement is unlikely. Squamous cell carcinomas respond more slowly; in some cases, it can take three weeks before any improvement is observed.

Total doses of **bleomycin** in patients not older than 60 years should not exceed 400 units (USP) (approximately 225 units/m² body surface), unless an examination of the lung function has ensured continued administration. Doses may need to be adjusted when given in combination with other antineoplastic agents or with radiotherapy, and in patients older than 60 years (see below).

Elderly patients

The total dose should be reduced as indicated below

Age in years	**Total dose**	**Dose per week**
80 and over	100 units (USP)	15 units (USP)
70-79	150-200 units (USP)	30 units (USP)
60-69	200-300 units (USP)	30-60 units (USP)
Under 60	400 units (USP)	30-60 units (USP)

Children

If administration of **bleomycin** to children is indicated, the dosage should be based on that recommended for adults and adjusted to body surface area.

Reduced renal function

In patients with reduced kidney function, doses should be reduced. If creatinine clearance decreases to 20 ml/min, 50% of **bleomycin** dose should be given.

Combination therapy

When used in combination with radiotherapy, the dose of **bleomycin** should be reduced. Dose adjustments may also be necessary in the context of combination chemotherapy.

Method of administration/preparation of solutions

Note: For preparation of the solution dissolve the whole content of a vial (15 units) in the appropriate amount of solvent. From this solution use an aliquot according to the units needed for treatment. Example: required dosage 8.5 units (5 units /m^2 x 1.7 m^2); dissolve the content of a vial (15 units) in 5 ml solvent; take out 2.83 ml (8.5 units) for application.

Intramuscular injection

Dissolve the contents of one vial in 1-5 mL physiological saline. Since repeated IM injections into the same site can lead to local reactions, it is advisable to change the injection site regularly. In case of excessive local reactions, a local anesthetic, e.g. 1.5 -2 mL lidocaine HCl 1% may be added to the solution for injection.

Intravenous injection

Dissolve the contents of a vial in 5-10 ml of physiological saline solvent and administer over a period of 5-10 minutes. Avoid a fast bolus injection, which will give a high blood concentration passing through the lungs, increasing the risk of damage to the lungs.

Intravenous infusion

Dissolve the contents of one vial in 200-1000 mL of physiological saline.

Intra-arterial injection

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

Intra-arterial infusion

Dissolve **bleomycin** in 200-1000 mL physiological saline. The infusion can be administered over a few hours to several days. Heparin may be added to prevent thrombosis at the injection site, especially if the infusion is administered over a long period of time.

Injection or infusion into an artery supplying the tumor tends to be more effective than other systemic routes of administration. The toxic effects are the same as those associated with intravenous injection or infusion.

Subcutaneous injection

Absorption after subcutaneous injection is delayed and may be similar to that associated with slow IV infusion. This method of administration is rarely used. Intradermal injection must be carefully avoided.

Intratumoral injection

Bleomycin is dissolved in physiological saline to make a 1-3 units (USP)/ml solution which is injected into the tumor and its surrounding tissues. This form of application is rarely used.

Intracavitary instillation

Following aspiration of the pleural or peritoneal cavity, **bleomycin** dissolved in physiological saline is instilled via the needle or catheter used for aspiration. The needle or catheter is then removed. In order to ensure the uniform dispersion of **bleomycin** within the serous cavity the patient's posture should be changed every 5 minutes, for 20 minutes.

Extravasal administration of **bleomycin** does not usually demand extraordinary precautions. In case of doubt (concentrated solution, sclerotic tissue, etc.) perfusion with physiological saline may be performed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

(idiosyncratic reaction with fever and chills, see section 4.4 "Special warnings and precautions for use").

Bleomycin is contraindicated in case of pulmonary infection, severe impairment of lung function, circulatory disorders of the lungs (e.g. pulmonary embolism, pulmonary fibrosis) and a history of bleomycin-induced lung injury.

Bleomycin is contraindicated during breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Patients receiving chemotherapy with **bleomycin** should be closely monitored by experienced oncologists.

A particularly strict benefit/risk assessment is required after pulmonary or mediastinal radiotherapy.

In case of renal impairment, **bleomycin** should only be used with particular caution and at a reduced dose.

Due to possible mutagenic effects of **bleomycin** on male and female germ cells, reliable contraception must be used during and for 6 months after the end of treatment.

Pulmonary reactions

Patients receiving treatment with **bleomycin** should be closely monitored for any signs of pulmonary dysfunction.

Pulmonary reactions are the most serious side effects and occur in approximately 10 % of treated patients either during or after the end of a treatment cycle. The most common form is interstitial lung disease. If not recognized and treated immediately, this can progress to pulmonary fibrosis. Approximately 1 % of treated patients die as a result of pulmonary fibrosis. Regular chest X-rays (preferably weekly) and lung function tests are recommended and should continue for 4 weeks after completion of a treatment cycle.

Pulmonary toxicity is both dose- and age- dependent; it is more common in patients over 70 years of age and those receiving a total dose greater than 400 units. It is significantly increased by thoracic radiotherapy and by hyperoxia during anesthesia for surgical procedures.

Pulmonary toxicity has also been observed occasionally in young patients receiving low doses.

Vascular changes occur in the lungs that lead to partial destruction of elastic components of the vessel wall. The earliest symptoms of bleomycin- induced lung injury are dyspnea and fine crackles. If pulmonary changes are noted, treatment must be discontinued until it is determined whether they are due to **bleomycin**. Patients should be given broad- spectrum antibiotics and corticosteroids.

Bleomycin sensitivity increases in older age.

If shortness of breath or pulmonary infiltrates occur that cannot be unequivocally attributed to the malignancy or concomitant pulmonary disease, **bleomycin** should be discontinued immediately and the patient treated with a corticosteroid and broad-spectrum antibiotics.

Although pulmonary toxicity of **bleomycin** appears to occur in a dose-dependent manner when the total dose exceeds 400 units (equivalent to approximately 225 units/m2 BSA) it may also be observed at lower doses, particularly in elderly patients, patients with impaired renal function, preexisting pulmonary disease, previous thoracic radiotherapy and patients requiring oxygen therapy.

Fever and chills

Like most cytotoxic agents, **bleomycin** can cause immediate or delayed toxicity. Fever on the day of injection is the most common immediate reaction.

Fever and chills are common. These sometimes occur 2-6 hours after the first injection. In cases of persistent high fever, administration of antipyretics may be required. The frequency of febrile episodes decreases with further injections.

Skin and mucous membranes

If cutaneous adverse reactions occur in AIDS patients, treatment should be discontinued and not resumed.

Induration, edema, hyperkeratosis, nail changes, formation of blisters on skin areas where there is prolonged pressure, e.g., the elbows, hair loss and stomatitis may also occur. These side effects are rarely serious and usually resolve after discontinuation of treatment.

Using **bleomycin** in combination with radiotherapy or other medications associated with mucosal damage appears to worsen stomatitis. Skin toxicity occurs relatively late and is correlated with the total dose; it usually develops in the second and third week after administration of 150 to 200 units (USP) of **bleomycin**.

Idiosyncratic reactions

An idiosyncratic reaction clinically similar to anaphylaxis has been reported in approximately 1% of patients treated with **bleomycin** for lymphoma. The reaction may occur immediately or after several hours, usually after the first or second dose. It manifests as hypotension, confusion, fever, chills, wheezing and stridor. Treatment is symptomatic and includes fluid replacement, vasopressors antihistamines and corticosteroids.

Hypersensitivity

Because of the possibility of an anaphylactoid reaction (in 1 % of patients with lymphoma, according to the literature), patients should start with a test dose of 1-2 units (USP). If no acute reaction occurs the regular dosage regimen can be administered.

Gastrointestinal tract

Gastrointestinal adverse reactions such as nausea and vomiting rare possible, but are more commonly observed with high-dose regimens. Antiemetics may be helpful. Loss of appetite and weight loss are common and may persist for an extended period beyond the end of treatment.

Blood and lymphatic system disorders

Acute myeloid leukaemia and myelodysplastic syndrome have been reported in patients who have received concomitant treatment with bleomycin and other antineoplastic agents.

Other

Vascular toxicity has been reported with the use of **bleomycin**, particularly in combination with other antineoplastic agents. Events are clinically inconsistent and include myocardial infarction, stroke, thrombotic microangiopathies such as hemolytic uremic syndrome and cerebral vasculitis. Like other cytotoxic agents, **bleomycin** can cause tumor lysis syndrome in patients with rapidly growing tumors. Appropriate supportive treatment and pharmacological measures may be able to prevent or mitigate such complications.

Pediatric population

Insufficient data are available on the use of **bleomycin** in children and adolescents. Until more information is available, **bleomycin** should only be administered to this patient group in exceptional cases and at dedicated centers. If its use is indicated, the individual doses specified in relation to BSA should be administered.

No studies have been conducted by Baxter Healthcare Corporation in children and adolescents.

4.5 Interaction with other medicinal products and other forms of interaction

If **bleomycin** is used as part of combination chemotherapy, its toxicity should be taken into account when selecting and dosing other agents with a similar spectrum of toxicity.

Careful case-specific assessment of the risks and benefits is required before any planned concomitant or sequential use of other agents or treatments that may increase the likelihood or severity of toxicity (as a result of pharmacodynamic or pharmacokinetic interactions). Patients treated with such combinations must be closely monitored for signs of toxicity to allow for early intervention.

An increased risk of pulmonary toxicity has been reported with concomitant use of BCNU, mitomycin, cyclophosphamide, methotrexate and gemcitabine.

Prior or concurrent thoracic radiotherapy contributes significantly to an increase in the frequency and severity of pulmonary toxicity.

Because of the potential of **bleomycin** to sensitize lung tissue, pulmonary toxicity increases when **bleomycin** is administered during surgical procedures requiring increased oxygen supplementation. The inspiratory O_2 concentration must therefore be reduced both intra- and postoperatively.

Raynaud like phenomena ranging from acral ischemia to necrosis of distal parts of the body (fingers, toes, tip of the nose) have been reported in patients with testicular cancer treated with a combination of **bleomycin** and vinca alkaloids.

A positive correlation between GFR (glomerular filtration rate) and lung function was observed in patients receiving combination therapy with cisplatin, vinblastine and **bleomycin. Bleomycin** should therefore be used with caution in patients with severe renal impairment. In another study, increasing doses of cisplatin were shown to be associated with a decrease in creatinine clearance and thus in the elimination of **bleomycin**.

Combination therapy with cisplatin in particular increases the pulmonary toxicity of **bleomycin**. Particular caution is therefore required with this combination. Data from the literature suggest that cisplatin should be administered after **bleomycin**.

An increase in the number of neutrophils and stimulation of the ability to produce oxygen free radicals after administration of granulocyte colony- stimulating factor may promote lung injury.

The rate and amount of absorption of oral acetyldigoxin and phenytoin may be decreased during treatment with **bleomycin**.

The bacteriostatic efficacy of gentamycin, amikacin and ticarcillin may be reduced.

Administration of live vaccines may result in severe to life-threatening infections in patients whose immune systems are compromised by chemotherapeutic agents, including **bleomycin**. Vaccination with live vaccines should be avoided in patients receiving **bleomycin**.

4.6 Fertility, pregnancy and lactation

Animal studies have shown that **bleomycin** has teratogenic, mutagenic, and carcinogenic properties.

Bleomycin should not be used during pregnancy, especially during the first trimester.

If critically indicated during the first trimester, a medical consultation regarding the termination of pregnancy is imperative.

If treatment cannot be delayed beyond the first trimester and the patient wishes to continue with the pregnancy, chemotherapy may be administered after informing the patient of the low but possible risk of teratogenic effects.

Bleomycin should not be used during breast-feeding; if necessary, breast-feeding should be discontinued.

Contraception:

Due to possible mutagenic effects of **bleomycin** on male and female germ cells, reliable contraception must be used during and for 6 months after the end of treatment.

There are no available data regarding effects on fertility.

4.7 Effects on ability to drive and use machines

Possible undesirable effects of chemotherapy with **bleomycin**, such as nausea and vomiting, may indirectly affect the patient's ability to drive and use machines.

4.8 Undesirable effects

Like most cytostatic agents, **bleomycin** can produce immediate and delayed toxic effects. The earliest reaction is fever on the day of the injection. Loss of appetite, fatigue and nausea may also occur. Pain at the injection site and in the region of the tumor has occasionally been observed. Other sporadic side effects include hypotension and local thrombophlebitis after intravenous injection.

Skin and mucosal changes, observed in up to 50% of treated patients, are the most common side effects. These manifest as erythema, pruritus, exanthema, striae, ulcerations, blistering, hyperpigmentation, and tenderness and swelling of the fingertips.

Bone marrow

Bleomycin does not appear to cause significant bone marrow depression. Thrombocytopenia associated with **bleomycin** has been attributed to increased platelet consumption rather than to decreased platelet formation.

In addition, Raynaud's phenomenon has been reported in association with **bleomycin** used as monotherapy and as part of combination therapy.

The following undesirable effects may occur during treatment with **bleomycin**:

Frequencies are defined as follows:
Very common (>1/10), common (≥1/100, <1/10), uncommon (≥1/1 000, <1/100), rare (≥1/10 000, <1/1 000), very rare (<1/10 000).

Primary system organ class	**Very common >1/10**	**Common ≥1/100– <1/10**	**Uncommon ≥1/1 000– <1/100**	**Rare ≥1/10 000– <1/1 000**	**Very rare <1/10 000**

Primary system organ class	Very common >1/10	Common ≥1/100– <1/10	Uncommon ≥1/1 000– <1/100	Rare ≥1/10 000– <1/1 000	Very rare <1/10 000
Blood and lymphatic system disorders			Myelosuppression Leukopenia Neutropenia Thrombocytopenia Bleeding	Febrile neutropenia	
Immune system disorders		Idiosyncratic reactions	Anaphylaxis Anaphylactoid reaction Hypersensitivity		
Nervous system disorders		Headache	Dizziness Confusion		
Cardiac disorders				Pericarditis Chest pain	
Vascular disorders			Hypotension	Myocardial infarction* Stroke Thrombotic microangiopathy Hemolytic uremic syndrome Cerebral vasculitis Raynaud's disease Arterial thrombosis Deep vein thrombosis	
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease Dyspnea	Pulmonary fibrosis* Acute respiratory distress syndrome (ARDS) Respiratory failure Pulmonary embolism			
Gastrointestinal disorders		Anorexia Weight-loss Nausea Vomiting Mucositis Stomatitis	Angular stomatitis Diarrhea		
Hepatobiliary disorders				Hepatic impairment Hepatitis	

Primary system organ class	Very common >1/10	Common ≥1/100– <1/10	Uncommon ≥1/1 000– <1/100	Rare ≥1/10 000– <1/1 000	Very rare <1/10 000
Skin and subcutaneous tissue disorders	Erythema Pruritus Striae Blistering Hyperpigmentation Tenderness and swelling of the fingertips	Exanthema Urticaria Erythema Induration Edema Hyperkeratosis Alopecia Dermatitis	Deformation and discoloration of the nails Blister formation over pressure points	Scleroderma	
Musculoskeletal, connective tissue and bone disorders			Muscle and limb pain		
Renal and urinary disorders			Oliguria Painful urination Polyuria Urinary retention		
General disorders and administration site conditions		Fever Chills Malaise	Pain in the tumor area Phlebitis Vein wall hypertrophy and venous access stenosis (with IV administration) Induration (with IM or topical administration)		Tumor lysis syndrome

*with a fatal outcome

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

It is virtually impossible to eliminate **bleomycin** from the body by dialysis. There is no specific antidote. Emergency procedures should include appropriate corrective and supportive measures.

Acute reactions associated with overdose manifest as hypotension, fever, tachycardia and generalized signs of shock. Treatment is exclusively symptomatic. In the event of respiratory complications, the patient should be treated with a corticosteroid and a broad-spectrum antibiotic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic antibiotics and related substances

ATC code: L01DC01

Bleomycin is a mixture of basic, water-soluble glycopeptide-antibiotics with cytotoxic activity. **Bleomycin** acts by interacting with both single and double-stranded DNA (deoxyribonucleic acid) leading to both single and double-strand scission, which in turn leads to inhibition of cell division, growth and DNA synthesis. **Bleomycin** can also influence RNA (ribonucleic acid) and protein biosynthesis to a lesser extent.

The tissue selectivity of **bleomycin** is primarily due to differences in intracellular inactivation. With their low content of **bleomycin** hydrolase, squamous epithelial cells are highly sensitive to **bleomycin**. Chromosome aberrations, such as fragmentation, chromatin strand breaks, and translocations occur in sensitive tissues, both healthy and neoplastic.

Bleomycin has pyrogenic properties.

Bleomycin causes little or no bone marrow toxicity and no immunosuppression.

Bleomycin can be used alone or in combination with radiotherapy or other cytostatic agents.

5.2 Pharmacokinetic properties

Absorption

Bleomycin is absorbed to a very limited extent after oral administration. After intravenous bolus injection of 15 units (USP)/m² BSA, maximum plasma levels of 1- 10 µg/mL are reached after around 10 minutes. After IM injection of 15 units, maximum plasma levels of around 1 µg /mL are reached after 30 minutes. Continuous infusion of 30 units (USP) **bleomycin** over 4- 5 days leads to a mean steady- state concentration in plasma of 100-300 ng/mL.

After intrapleural or intraperitoneal use, **bleomycin** is absorbed systemically. After intrapleural administration, approximately 45% of the dose is absorbed into the circulation.

Distribution

Bleomycin is rapidly distributed in the tissues and the highest concentrations are reached in the skin, lungs, peritoneum and lymphatic system. Low concentrations are found in the bone marrow. **Bleomycin** is undetectable in CSF after intravenous injection. **Bleomycin** crosses the placenta. **The apparent volume of distribution** $(V_d)_ß$ is assumed to be about 0.27±0.09 L/kg. The plasma protein binding of **bleomycin** is minimal.

Biotransformation

Inactivation is effected by hydrolases, which have been detected in the plasma, liver, spleen, intestine and bone marrow. In contrast, the enzymatic activity of hydrolases in the skin and lungs is low.

Elimination

The elimination half-life (T ½ ß) is around 3 hours. After continuous IV infusion, the elimination half-life may increase to 9 hours. The systemic plasma clearance (Cl_S) is around 1.1 mL/min x kg bodyweight. Approximately 2/3 of the administered dose is excreted unchanged in the urine, probably by glomerular filtration.

After IV or IM injection, about 50% of the active substance is recovered in the urine. .In renal impairment , the half-life is considerably prolonged so that dose reductions are required. When creatinine clearance is <35 mL/min, renal excretion decreases to less than 20% and plasma levels may be increased. Previous observations show that **bleomycin** is barely if at all eliminated by dialysis.

5.3 Preclinical safety data

Animal studies have shown that **bleomycin** has teratogenic, mutagenic and carcinogenic properties.

Animal studies show that **bleomycin** accumulates in the skin, lungs, peritoneum and lymphatic tissue, which explains the particular sensitivity of these tissues to **bleomycin** (see also section 4.3 "Contraindications" and section 4.4 "Special warnings and precautions for use")

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Bleomycin must not be mixed with solutions of essential amino acids, riboflavin, ascorbic acid, dexamethasone, aminophylline, benzylpenicillin, carbenicillin, cefalotin, cefazoline, diazepam, glutathione, hydrogen peroxide, hydrocortisone sodium succinate, methotrexate, mitomycin, nafcillin, penicillin G, or substances containing sulfhydryl groups, terbutaline, thiols.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6 (Special precautions for disposal and other handling).

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
For one-time use only.
Discard any unused solution!

6.4 Special precautions for storage

Store at 2 -8°C. Keep in original package.

Shelf life after reconstitution: 24 hours at 25ºC. Compatible with: Physiological saline.

6.5 Nature and contents of container

Packs with 1 or 10 vials (Type 1 colorless glass with rubber stopper and light green aluminum cap) each containing **bleomycin** sulphate equivalent to 15 units (USP)

6.6 Special precautions for disposal and other handling

Safe handling:

The general guidelines for the safe handling of cytotoxic drugs should be followed. Appropriate precautions should be taken to avoid contact with skin, mucous membranes and eyes. In case of contamination, the affected body parts should be rinsed thoroughly with water.

Protective clothing must be worn when handling urine produced up to 72 hours after administration of **bleomycin**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for preparation of the solution for injection/infusion:
Note: To prepare a solution, dissolve the entire contents of one vial (15 units) in the appropriate amount of solvent. Then take the number of units required for treatment from this batch.

Example: Required dose 8.5 units (5 units/m^2 BSA = 5 units x 1.7); dissolve the contents of one vial (15 units) in 5 mL solvent; withdraw 2.83 mL (8.5 units) for use.

Intramuscular injection
Dissolve the contents of one vial in 1–5 mL physiological saline.
In case of excessive local reactions, a local anesthetic, e.g., 1.5–2 mL lidocaine HCl 1% may be added to the solution for injection.

Intravenous injection
Dissolve the contents of one vial in 5–10 mL physiological saline.

Intravenous infusion
Dissolve the contents of one vial in 200–1 000 mL physiological saline.

Intraarterial injection
Dissolve the contents of one vial of **bleomycin** in at least 5 mL physiological saline.

Intraarterial infusion
Dissolve **bleomycin** in 200–1 000 mL physiological saline. Heparin may be added to prevent thrombosis at the injection site, especially if the infusion is administered over a long period of time.

Subcutaneous injection
Absorption after subcutaneous injection is delayed and may be similar to that associated with slow IV infusion. This method of administration is rarely used. Intradermal injection must be carefully avoided.

Intrapleural instillation
After thoracentesis, **bleomycin** dissolved in a physiological saline solution is instilled via the puncture cannula or drainage catheter. The cannula or catheter is then removed. To ensure the uniform distribution of **bleomycin** in the serous cavity, the position of the patient should be changed every 5 minutes for a period of 20 minutes.

Intratumoral injection
Bleomycin is dissolved in physiological saline to a concentration of 1–3 units/mL.

7. MANUFACTURER

Baxter Oncology GmbH, Halle Westfalen, Germany

8. REGISTRATION HOLDER

MegaPharm Ltd.,

15 Ha'tidhar street, Ra'anana, Israel.

9. MARKETING AUTHORISATION NUMBER

133-57-25199-00

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