Bleomycin – Summary of Product Characteristics

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**.

1. NAME OF THE MEDICINAL PRODUCT

Bleomycin PFI

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains **Bleomycin** sulphate equivalent to 15 units (USP) or 15000 International Units (I.U) **Bleomycin**. 1 unit (USP) (corresponding to 1000 I.U.) corresponds to 1 mg potency. Note 1 mg potency is defined by bioassay and, therefore, is not identical to 1 mg dry weight (1 mg dry **weight** according USP corresponds to 1.5 to 2.0 mg potency).

3. PHARMACEUTICAL FORM

Powder for solution for infusion, injection or instillation.

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-seminomas).
4) Malignant effusions of serous cavities (pleura and peritoneum).
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 as 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 for 6-24 hours of 10-15 units (USP)/m²/day in 4 to 7 consecutive days every 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. Because of the possibility of an anaphylactoid reaction, lymphoma patients should be treated with 1-2 units (USP)/dose for the first two doses. 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 once or twice a week. Intravenous infusion for 6-24 hours of 15-20 units (USP)/m²/day for 5-6 consecutive days every 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.
Improvement of Hodgkin's disease and testicular tumors is prompt and noted within two weeks. If no improvement is seen by this time, improvement is unlikely. Squamous cell cancers respond more slowly, sometimes requiring as long as 3 weeks before any improvement is noted.

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)

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

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
In conjunction with radiotherapy the **Bleomycin** dosage should be reduced. The dose may need to be adjusted when **Bleomycin** is used in combination with other cytotoxic drugs.

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 a vial in 1-5 ml physiological saline solvent. Since repeated i.m. injections at the same site may cause local discomfort, it is advisable to change the injection site. In case of undue local discomfort, a local anaesthetic such as 1 ½ -2 ml 1% lidocaine hydrochloride can be added to the injection solution.

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 **Bleomycin** in 200-1000 ml of physiological saline.

Intra-arterial injection
Dissolve the contents of a vial of **Bleomycin** in 5 ml or more of physiological saline and administer over a period of 5-10 minutes.

Intra-arterial infusion
Dissolve **Bleomycin** in 200-1000 ml of physiological saline. The infusion may be given over a few hours to several days. To prevent thrombosis at the injection site heparin can be administered, especially if an infusion is given over a long period of time.

Injection/infusion into the artery supplying the tumor shows a tendency for higher efficacy than other routes of systemic administration. The toxic effects are as with i.v. injection/infusion.

Subcutaneous injection
Absorption after subcutaneous injection is delayed and may imitate slow i.v. infusion; this form of administration is not used so often. Care must be taken to avoid intradermal injection.

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 Contra-indications

Bleomycin is contra-indicated in patients with acute pulmonary infection, severely impaired lung function or circulatory disturbances in the lungs and in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to the drug (Pregnancy and lactation: see item 4.6).

4.4 Special warnings and special precautions for use

Patients receiving **Bleomycin** chemotherapy should be carefully monitored by experienced oncologists.

Because of the possible teratogenic effect of **Bleomycin** on male and female germ cells adequate conception control should be established during, and for a period of 6 months after treatment.

Pulmonary Reactions
Patients undergoing treatment with **Bleomycin** should be carefully monitored for any sign of lung dysfunction. Pulmonary reactions are the most serious side effects, occurring in approximately 10 % of treated patients during, or occasionally after a course of treatment. The most frequent form is interstitial pneumonitis. If not diagnosed and treated immediately this condition may progress to pulmonary fibrosis. Approximately 1 % of patients treated died because of pulmonary fibrosis. Frequent chest X-rays (preferably weekly) are advisable and should be continued for up to 4 weeks after completion of a course of treatment.

Pulmonary toxicity of **Bleomycin** is both dose-related and age-related when the total dose exceeds 400 units (USP) (approximately 225 units/m² body surface) this may also occur when lower doses are administered, especially in elderly patients (over 70 years of age), 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 anesthesia. Pulmonary toxicity is unpredictable and has been seen occasionally in young patients receiving low doses. Vascular changes occur in the lung, partly destroying the elasticity of the walls of the vessel. The earliest symptom associated with pulmonary toxicity of **Bleomycin** is dyspnea. 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.

Bleomycin sensitivity increases in old age. If breathlessness or lung infiltrates appear, not obviously attributable to tumor or to co-existent lung disease, administration of the drug must be stopped immediately and patients should be treated with corticosteroid and broad-spectrum antibiotics.

Pyrexia
Like most cytotoxic agents **Bleomycin** can cause immediate and delayed toxic effects. The most immediate effect is fever on the day of injection. It sometimes occurs 2 to 6 hours after the first injection of **Bleomycin**. In cases of persistent severe pyrexia it may be necessary to give antipyretics. The incidence of pyrexia decreases with subsequent injections.

Skin and mucous changes
In the event of cutaneous side effects in patients with AIDS, **Bleomycin** treatment should be stopped and should not be resumed.

Induration, edema, hyperkeratosis, nail changes, bulla formation over pressure points such as elbows, alopecia and stomatitis may occur during treatment with **Bleomycin**.

These side effects are rarely serious and usually disappear after completion of treatment. Mucosal ulceration seems to be aggravated when **Bleomycin** is combined with irradiation or other drugs toxic to mucous membranes. Skin toxicity is a relatively late manifestation correlating with the cumulative doses, usually developing in the 2nd and 3rd week of treatment 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 the lymphoma patients treated with **Bleomycin**. The reaction may be immediate or delayed for several hours, and usually occurs after the first or second dose. It consists of hypotension, mental confusion, fever, chills, and wheezing. Treatment is symptomatic, including volume expansion, pressor agents, antihistamines, and corticosteroids.

Hypersensitivity
Because of the possibility of an anaphylactoid reaction (reported in 1 % of lymphoma patients) patients should receive initially a test dose of 1 -2 units (USP) in total. If no acute reaction occurs the regular dosage regimen can be administered.

Gastrointestinal
Gastrointestinal side effects such as nausea and vomiting may occur but are more often seen in high-dose schedules. Antiemetic drugs may be of help. Anorexia and weight loss are common and may persist for a long time after termination of the treatment.

Others
Vascular toxicities have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathies like hemolytic-uremic-syndrome and cerebral arteritis.

Like other cytotoxic agents, **Bleomycin** may induce tumor lysis syndrome in patients with rapidly growing tumors. Adequate supporting treatment and pharmacological measures may prevent or relieve such complications.

4.5 Interactions with other medicinal products and other forms of interaction

When **Bleomycin** is used as one of the drugs in multiple chemotherapy regimens the toxicity of **Bleomycin** should be borne in mind in the selection and dosage of drugs with a similar toxic potential.
An increased risk of pulmonary toxicity has been described with concomitant use of BCNU, mitomycin-C, cyclophosphamide, methotrexate and gemcitabine.

Previous or concurrent radiotherapy to the chest is an important factor in increasing the incidence and severity of lung toxicity.
Because of the potential of **Bleomycin** to sensitize the lung tissue, the risk of developing pulmonary toxicity is increased in patients who have received **Bleomycin** when oxygen is being administered at surgery. A reduction in inspired oxygen during operation and postoperatively is therefore recommended.

In patients treated for testicular cancer with a combination of **Bleomycin** and vinca alkaloids a syndrome has been reported corresponding to morbus Raynaud, ischemia which may lead to necrosis of the peripheral parts of the body (fingers, toes, nose tip).
In patients treated with a triple combination regimen of cisplatin, vinblastine and **Bleomycin**, a positive correlation between GFR (glomerular filtration rate) and pulmonary function was observed. Therefore, **Bleomycin** should be used cautiously in patients with severely impaired renal function. Another study showed that an increase of the cisplatin dose was associated with a decrease of the creatinine clearance and the **Bleomycin** elimination.
The increase in neutrophil counts and the stimulation of the ability to produce superoxide radicals after the use of granulocyte-colony stimulating factor may potentiate lung injury.
The rate and extent of absorption of oral acetyldigoxin and of phenytoin could be reduced by **Bleomycin** treatments.

4.6 Use during pregnancy and lactation

Animal experiments have revealed that **Bleomycin** has teratogenic and carcinogenic potential.
The use of **Bleomycin** should be avoided whenever possible during pregnancy particularly during the first trimester.
In a vital indication during the first trimester of pregnancy a medical consultation regarding abortion is absolutely necessary.
After the first trimester of pregnancy, if therapy can not be delayed and the patient wishes to continue with her pregnancy, chemotherapy may be undertaken after informing the patient of the minor but possible risk of teratogenic effects.
Bleomycin should not be given to mothers who are breast feeding.

Contraceptive measures:
Bleomycin can cause congenital anomalities. 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

Potential side effects of the chemotherapy with **Bleomycin**, like nausea and vomiting may indirectly impair the patient's ability to drive or to use machines.

4.8 Undesirable Effects

NEOPLASMS, BENIGN AND MALIGNANT AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS): Tumor pain, Tumor lysis syndrome

BLOOD AND LYMPHATIC SYSTEM DISORDERS:
Febrile neutropenia, Neutropenia, Thrombocytopenia, Hemolytic uremic syndrome, Thrombotic microangiopathy, Granulocytopenia, Leukopenia

METABOLISM AND NUTRITION DISORDERS:
Anorexia

PSYCHIATRIC DISORDERS:
Confusional state

NERVOUS SYSTEM DISORDERS:
Cerebral arteritis, Cerebrovascular accident

CARDIAC DISORDERS:
Myocardial infarction, Pericarditis

VASCULAR DISORDERS:
Hypotension, Phlebitis, Raynaud's phenomenon, Thrombophlebitis, Arterial thrombosis, deep vein thrombosis.

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS:
Respiratory failure, pulmonary embolism, Dyspnoea, Interstitial lung disease, Pulmonary fibrosis, Pulmonary toxicity, Rales, Wheezing, Acute respiratory distress syndrome.

GASTROINTESTINAL DISORDERS:
Nausea, Stomatitis, Vomiting

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Alopecia, Blister, Erythema, Hyperkeratosis, Nail disorder, Pruritis, Rash, Rash vesicular, Skin hyperpigmentation, Skin striae, Skin toxicity, Dermatitis, Drug eruption.

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS:
Arthralgia, Myalgia, Scleroderma

GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS:
Chest pain, Chills, Induration, Injection site pain, Local reaction, Mucosal inflammation, Mucosal ulceration, Oedema, Oedema peripheral, Pyrexia, Tenderness, Idiosyncratic drug reaction

4.9 Overdose

Observations indicate that it is difficult to eliminate **Bleomycin** from the body by dialysis.The acute reaction following 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 problems the patient should be treated with a corticosteroid and a broad-spectrum antibiotic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC-code: L 01 DC 01
Bleomycin is a mixture of basic, water-soluble glucopeptide-antibiotics with cytotoxic activity. **Bleomycin** acts by intercalating with both single and double-stranded DNA (deoxyribonucleic acid) resulting in both single and double-strand scission, leading to inhibition of cell division, of growth and of DNA synthesis; to a lesser degree **Bleomycin** may influence RNA (ribonucleic acid) and protein synthesis.

The most important factor in the tissue selectivity of **Bleomycin** is the difference in intracellular inactivation. Squamous cells, with their low content of **Bleomycin** hydrolase, have a high susceptibility for **Bleomycin**. In sensitive tissues, both normal and neoplastic, chromosome aberrations such as fragmentation, chromatide breaks, and translocations appear to be regularly produced.
Bleomycin is pyrogenic.
Bleomycin causes little or no bone-marrow toxicity and no immunosuppression.
Bleomycin can be used alone, in combination with radiotherapy and together with other cytotoxic drugs.

5.2 Pharmacokinetic properties

Absorption
Bleomycin is administered parenterally. After intravenous administration of a bolus dose of 15 units (USP)/m² body surface peak concentrations of 1 to 10 mU/ml are achieved in plasma. Following the i.m. injection of 15 units peak plasma concentrations of about 1 mU/ml are achieved after 30 minutes. Continuous infusion of 30 units (USP) of **Bleomycin** daily for 4 to 5 days resulted in an average steady state plasma concentration of 100-300 µU/ml.

Distribution
Bleomycin is rapidly distributed to body tissues with highest concentrations in skin, lungs, peritoneum and lymphatic tissue. 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 apparent volume of distribution (Vd)ß is about 0.27±0.09 L/kg. **Bleomycin** is bound to plasma proteins only to a slight extent.

Biotransformation
The biotransformation of **Bleomycin** is not fully mapped out. Inactivation takes place during enzymatic break down by **Bleomycin** hydrolase which is localized primarily in plasma, liver, spleen, intestine and bone marrow and to a much lesser extent in skin and lungs.

Elimination
The elimination half-life (T ½ ß) of **Bleomycin** is about 3 hours. After continuous i.v. infusion the elimination half-life may be increased to about 9 hours. The systemic plasma clearance (Cls) is about 1.1 ml/min x kg. 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 24 hours after an i.v. or i.m. injection. Therefore, the rate of excretion is highly influenced by renal function; concentrations in plasma are significantly 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** has teratogenic and carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Bleomycin solution should not be mixed with solutions of essential amino acids, aminophylline, ascorbic acid, benzylpenicilline, carbenicilline, cefalotine, cefalozine, dexamethasone, diazepam, glutathione, hydrogen superoxide, hydrocortisone-Na -succinate, methotrexate, mitomycin, nafcilline, penicilline G, riboflavin, substances containing sulfhydryl groups, terbutaline, or thiols.

6.3 Shelf life

42 months (3,5 years).

6.4 Special precautions for storage

Store at 2 -8°C. Keep in the carton.

6.5 Nature and contents of container

Packs with 1 or 10 vials each containing **Bleomycin** sulphate equivalent to 15 units (USP).

6.6 Instructions for use/handling

The general guidelines for safe handling of cytotoxic drugs should be followed. Precautions should be taken to avoid contact with skin, mucous membranes or eyes. In the event of contamination the affected parts should be washed thoroughly with water. Urine produced for up to 72 hours after a dose of **Bleomycin** should be handled by wearing protective clothing

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8. MANUFACTURER

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9. REGISTRATION HOLDER

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