

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bleomycin Venus Pharma 15,000 IU Powder for Solution for Injection / Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Bleomycin Sulfate equivalent to Bleomycin 15,000 IU

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection / infusion

White or cream-coloured, lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bleomycin can be used in the treatment of:

- Squamous cell carcinoma (SCC) of the head and neck, cervix and external genitalia
- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma of intermediate and high malignancy in adults
- Testicular carcinoma (seminoma and non-seminoma)
- Intrapleural therapy of malignant pleural effusions

Bleomycin can be used as a monotherapy, but is usually combined with other cytostatics and/or radiation therapy.

4.2 Posology and method of administration

Warning: Posology for all therapeutic indications is provided in IU and not in mg. Some hospital protocols may state use “mg” instead of Units (U or IU). This mg value refers to mg-activity and not to mg-dry material as these reflect different values.

Our recommendation is to ignore this posology in mg and actually use the posology in International Units (IU) as described in this SmPC for the relevant therapeutic indications.

Please note that 1 mg dry substance is equivalent to at least 1500 IU. Yet we strongly recommend **not to use** this conversion as this may result in overdosage because of the differences between mg-activity and mg-dry material. This product should therefore only be prescribed in international units (IU).

Bleomycin should only be used under the strictest supervision of a physician specialised in the use of oncolytic medicinal products, preferably in a hospital with experience in such therapies

Bleomycin may be administered intravenously, intramuscularly, intra-arterially, subcutaneously or by intrapleural instillation. Local injection directly into the tumour may occasionally be indicated.

Posology

Adults

1) *Squamous cell carcinoma*

Intramuscular or intravenous injection of $10\text{-}15 \times 10^3$ IU/m² body surface area (BSA), once or twice a week, at intervals of 3-4 weeks up to a lifetime cumulative dose of 360×10^3 IU.

Intravenous infusion of $10\text{-}15 \times 10^3$ IU/m²/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/m² BSA, once or twice a week, up to a cumulative total dose of 225×10^3 IU. Because of the possibility of anaphylactoid reactions, lymphoma patients should be treated with lower doses (for instance 2×10^3 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/m² BSA once or twice a week, at intervals of 3-4 weeks up to a total cumulative dose of 400×10^3 IU. The intravenous infusion of the dose of $10\text{-}15 \times 10^3$ IU/m² BSA/day is performed for 6-24 hours on 5-6 consecutive days, at intervals of 3-4 weeks.

4) *Malignant pleural effusions*

60×10^3 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 lifetime 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 400×10^3 IU (corresponding to 225×10^3 IU/m² 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 225×10^3 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 observed.

Elderly population (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	100×10^3 IU	15×10^3 IU
70-79	$150\text{-}200 \times 10^3$ IU	30×10^3 IU
60-69	$200\text{-}300 \times 10^3$ IU	$30\text{-}60 \times 10^3$ IU
Under 60	400×10^3 IU	$30\text{-}60 \times 10^3$ IU

Paediatric population

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 specialised protocols and guidelines should be consulted for the appropriate treatment regimen.

Renal impairment

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 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

Method of administration and preparation of the solution for injection/infusion (see also section 6.6)

N.B.: The entire contents of a vial (15,000 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.

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, is 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, the position of the 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 the 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

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1
- Ataxia telangiectasia
- Pulmonary infection, severely impaired lung function or a history of lung damage caused by bleomycin
- Breastfeeding (see section 4.6)

4.4 Special warnings and precautions for use

Patients receiving Bleomycin chemotherapy must be carefully monitored by experienced oncologists.

A highly rigorous risk/benefit assessment should be performed following lung or mediastinal radiotherapy. Bleomycin should only be used with caution and at a reduced dose in the event of impaired renal function. Because of the possible mutagenic effects of bleomycin on male and female germ cells, reliable contraception must be ensured during therapy and for up to 6 months after the end thereof.

Pulmonary reactions

Patients should be carefully monitored for any signs of pulmonary dysfunction during treatment with bleomycin

Pulmonary reactions are the most serious side effects, occurring in roughly 10% of patients treated, during or after the end of a course of treatment. The most common form is interstitial pneumonitis. If this condition is not recognised and treated promptly, it can develop into pulmonary fibrosis. Approximately 1% of patients treated have died from the consequences of pulmonary fibrosis.

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. With concomitant radiation therapy of the thorax, a study or an X-ray of the thorax should possibly be done more frequently.

Lung function tests with 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. Monthly analysis of pulmonary diffusion capacity for carbon monoxide could be planned. A study of lung function, in particular the measuring of the carbon monoxide diffusion and vital capacity, often makes an early diagnosis of lung toxicity possible.

Pulmonary toxicity is both dose-related and age-related, occurring more frequently in those over the age of 70 and in patients who have received a total dose of more than 400 units. It is significantly increased by thoracic irradiation and by hyperoxia during surgical anaesthesia.

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

Vascular changes occur in the lungs, leading to partial destruction of the elasticity of the vessel wall. The earliest symptom of pulmonary damage caused by bleomycin is dyspnoea. Fine rales are the earliest sign. If pulmonary changes are noticed, bleomycin treatment should be discontinued until it is determined whether they are caused by the medication. The patients should be treated with broad spectrum antibiotics and corticosteroids.

In the event of dyspnoea, cough, basal crepitations or lung infiltrates not clearly attributable to the neoplasm or a concomitant pulmonary disease, administration of bleomycin must be discontinued immediately and the patient should be treated with a corticosteroid and broad spectrum antibiotics. High oxygen concentrations should be used with caution. In case of lung damage as a result of bleomycin, bleomycin should not be administered any more (see section 4.3).

Although the pulmonary toxicity of bleomycin appears to be dose-related upon exceeding a total dose of 400 units (corresponding to approx. 225 units/m² BSA), it can also be observed at lower doses, in particular in elderly patients, patients with impaired renal function patients with pre-existing lung disease, patients with a history of or receiving concomitant thoracic radiotherapy, and patients requiring oxygen administration. These patients should be carefully monitored and the bleomycin dosage reduced or the dose interval prolonged based on clinical observation of the patient. Bleomycin should be used with extreme caution in patients with lung cancer as these patients show an increased incidence of pulmonary toxicity

As 2/3 of the administered dose of bleomycin is excreted unchanged in the urine, renal function has a major effect on the rate of excretion. Plasma concentrations are significantly elevated when usual doses are administered to patients with renal function disorders.

Other clinical conditions requiring caution include patients with severe heart disease or hepatic dysfunction as toxicity may be increased and patients with varicella as fatal systematic dysfunctions may occur.

Idiosyncratic reactions/ hypersensitivity

Idiosyncratic reactions, clinically similar to anaphylaxis, have been reported in approximately 1% of lymphoma patients treated with bleomycin. The reaction may be immediate or after a few hours delay, and usually occurs after the first or second dose. It consists of hypotension, confusion, fever, chills, wheezing and stridor. Treatment is symptomatic and comprises volume expansion, vasopressors, antihistamines and corticosteroids.

Because of the possibility of an anaphylactoid reaction (in 1% of lymphoma patients, according to the literature), patients should initially receive a test dose of 1-2 units. If there is no acute reaction, the full dose can be administered.

Miscellaneous

There have been reports of vascular toxicity following use of bleomycin, in particular in combination with other antineoplastic agents. The events are clinically heterogeneous and include myocardial infarction, cerebrovascular insults, thrombotic microangiopathies, e.g. haemolytic uraemic syndrome and cerebral arteritis.

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

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.

Patients with creatinine clearance values of less than 50 mL/min should be treated with caution and their renal function should be carefully monitored during the administration of bleomycin. Lower doses of bleomycin may be required in these patients than those with normal renal function (see section 4.2).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Combination chemotherapy

If bleomycin is used as part of combination chemotherapy, its toxicity should be taken into account for the selection and dosage of other agents with a similar toxicity spectrum.

An increased risk of pulmonary toxicity has been reported with concomitant administration of other agents with pulmonary toxicity, e.g. BCNU, mitomycin, cyclophosphamide, methotrexate and gemcitabine. The pulmonary toxicity of bleomycin is potentiated by combined treatment with cisplatin in particular. Special care should therefore be taken with this combination. Data from the literature indicates that cisplatin should only be administered after bleomycin.

In patients with testicular tumours treated with a combination of bleomycin and vinca alkaloids, Raynaud- like phenomena have been reported with acral ischemia, leading to necrosis of peripheral parts of the body (fingers, toes, tip of the nose).

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

Radiotherapy

Previous or concurrent thoracic radiotherapy contributes significantly to increased frequency and severity of pulmonary toxicity

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.

Oxygen concentration

Because of bleomycin's potential to sensitise the lung tissue, pulmonary toxicity increases if bleomycin is administered during surgical procedures involving increased oxygen supply. The inspiratory O₂ concentration should therefore be reduced intraoperatively and postoperatively.

Granulocyte Colony-Stimulating Factor (GCSF)

An increase in the number of neutrophil granulocytes and stimulation of the ability to generate free oxygen radicals following administration of GCSF may potentiate lung injury.

Digoxin

These are case reports of a reduced effect of digoxin as a result of a reduced oral bioavailability when combined with bleomycin.

Phenytoin and phosphentoin

There are case reports of reduced levels of phenytoin when combined with bleomycin. Risk of exacerbation of convulsions resulting from the decrease of phenytoin digestive absorption by cytotoxic medicinal products or risk of toxicity enhancement or loss of efficacy of the cytotoxic medicinal product due to increased hepatic metabolism by phenytoin. Concomitant use is not recommended.

Clozapine

Concomitant use of bleomycin with clozapine should be avoided due to an increased risk of agranulocytosis.

Antibiotics

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

Ciclosporine, tacrolimus

Excessive immunosuppression with risk of lymphoproliferation exists.

Live vaccines

The administration of live vaccines may lead to serious or life-threatening infections in patients whose immune system is weakened by chemotherapy agents, including bleomycin. Vaccinations with live vaccine should be avoided in patients receiving bleomycin. Use inactivated vaccine where this exists (poliomyelitis). Vaccination with the yellow fever vaccine has resulted in severe and fatal infections when used in combination with immunosuppressive chemo therapeutics. This risk is increased in subjects who are already immunosuppressed by their underlying disease. This combination must not be used.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data on the use of bleomycin in pregnant women. Studies in animals have shown reproduction toxicity (see section 5.3). On the basis of the results of animal studies and the pharmacological efficacy of the product, there is a potential risk of embryonic and foetal abnormalities. Bleomycin will pass the placenta.

Bleomycin should therefore not be used during the pregnancy, unless it is strictly necessary, particularly during the first trimester.

If pregnancy occurs during treatment, the patient should be informed about the risks for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered.

Women of childbearing potential/contraception in males and females

Both male and female patients should take adequate contraceptive measures up to six months after the discontinuation of the therapy.

Genetic counselling is also recommended for patients wishing to have children after therapy.

Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with bleomycin.

Breast-feeding

It is unknown if Bleomycin or the metabolites are excreted in the mother's milk. Due to possible very harmful effects on the infant, breast-feeding during treatment with bleomycin is contraindicated.

Fertility

Bleomycin therapy may cause irreversible infertility.

4.7 Effects on ability to drive and use machines

Possible side effects of chemotherapy with bleomycin, e.g. nausea and vomiting, may indirectly affect the patient's ability to drive or use machines

4.8 Undesirable effects

a. Summary of the safety profile

Like most cytotoxic agents, bleomycin can cause immediate and delayed toxic effects. Fever on the day of injection is the earliest reaction. 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%). Pain at the injection site and in the tumour area has also been observed on occasion. Other sporadic side effects include hypotension and local thrombophlebitis following intravenous injection.

There have also been reports of Raynaud's phenomena, both when using bleomycin as monotherapy and in combination therapy

b. Tabulated list of adverse reactions:

The following undesirable effects can occur during treatment with bleomycin:

Frequencies are defined as follows:

Very common ($\leq 1/10$); common ($\leq 1/100$ to $< 1/10$); uncommon ($\leq 1/1,000$ to $< 1/100$); rare ($\leq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$), not known (cannot be estimated from the available data).

Primary system organ classes	Very common $\geq 1/10$	Common $\geq 1/100$ - $< 1/10$	Uncommon $\geq 1/1,000$ - $< 1/100$	Rare $\geq 1/10,000$ - $< 1/1,000$	Very rare $< 1/10,000$	Not known
Infections and infestations						Sepsis

Neoplasms, Benign, Malignant and Unspecified (including Cysts and Polyps)			Tumour pain			
Blood and lymphatic system disorders			Myelosuppression, Leukopaenia, Neutropaenia, Thrombocytopenia, Haemorrhage	Febrile neutropaenia		Pancytopenia, Anaemia
Immune system disorders		Anaphylaxis, Hypersensitivity, Idiosyncratic drug reactions				
Nervous system disorders		Headache	Dizziness, Confusion			
Cardiac disorders				Myocardial infarction, Pericarditis, Chest pain		
Vascular disorders			Hypotension	Cerebral infarction, Thrombotic microangiopathies, Haemolytic uraemic syndrome, Cerebral arteritis, Raynaud's phenomena, Arterial thrombosis, Deep vein thrombosis		Peripheral ischaemia
Respiratory, thoracic and mediastinal disorders	Interstitial pneumonitis, Pulmonary fibrosis,	Acute respiratory distress syndrome				

	Dyspnoea	(ARDS), Lung failure, Pulmonary embolism				
Gastrointestinal disorders	Decreased appetite, Weight loss, Nausea, Vomiting, Mucositis, Stomatitis		Angular cheilitis, Diarrhoea			
Hepatobiliary disorders				Hepatic impairment		
Skin and subcutaneous tissue disorders	Erythema, Pruritus, Striae, Blistering, Hyperpigmentation, Tenderness and swelling of the fingertips, Hyperkeratosis, Hair loss	Exanthema, Urticaria, Skin reddening, Induration, Oedema, Flagellate dermatitis	Deformation and discolouration of the nails, Bulla formation at pressure points	Scleroderma		
Musculoskeletal and connective tissue disorders			Muscle and joint pain			
Renal and urinary disorders			Oliguria, Dysuria, Polyuria, Urinary retention			
General disorders and administration site conditions		Pyrexia, Chills, Malaise	Pain in the tumour area, Phlebitis, Hypertrophy of the vein wall and venous access constriction (with i.v. administration), Induration (with		Tumour lysis syndrome	

		i.m. or local administration)		
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c. Description of selected adverse reactions

Fever and chills may develop with a lag time of 45 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.

If cutaneous side effects occur in AIDS patients, the treatment should be discontinued and not resumed. Skin and mucosal lesions are the most common undesirable effects and are observed in up to 50% of the patients treated. They comprise induration, oedema, erythema, pruritus, rashes, striae, ulceration, blistering, hyperpigmentation, tenderness, swelling of the fingertips, hyperkeratosis, nail changes, bulla formation at pressure points such as the elbows, hair loss and stomatitis.

Mucosal ulcers appear to be aggravated by the combination of bleomycin with radiotherapy or other medication toxic to mucous membranes. Skin toxicity occurs at a relatively late stage and is correlated with the total dose; it usually develops in the second and third week after administration of 150 to 200 units of bleomycin.

Gastrointestinal side effects such as nausea and vomiting are possible, but are observed more frequently in high-dose regimens. Antiemetics may be helpful. Loss of appetite and weight loss are common and may continue for a long time after the end of the treatment.

Bone marrow

Bleomycin does not appear to have any significant bone marrow depressant properties. Thrombocytopaenia occurring in connection with bleomycin treatment has not been attributed to decreased production of platelets, but rather to increased destruction of platelets.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 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.

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 leads in turn to inhibition of cell division, inhibition of growth and inhibition of DNA synthesis. Bleomycin can also influence RNA (ribonucleic acid) and protein biosynthesis to a lesser extent.

The main factor in the tissue selectivity of Bleomycin is differences in intracellular inactivation. Squamous cells, with their low bleomycin hydrolase content, are highly sensitive to Bleomycin. Chromosome aberrations such as fragmentation, chromatid breaks, and translocations occur in sensitive tissues, both healthy and neoplastic.

Bleomycin can be pyrogenic. It causes little or no bone-marrow toxicity and no immunosuppression.

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

5.2 Pharmacokinetic properties

Absorption

Bleomycin is absorbed to a very limited extent orally. Following intravenous bolus injection of 15×10^3 IU/m² BSA, peak plasma concentrations of 1-10 IU are reached after approximately 10 minutes. Following i.m. injection of 15×10^3 IU, maximum plasma levels of approximately 1 IU are reached after 30 minutes. Continuous infusion of 30×10^3 IU of bleomycin over 4-5 days results in an average steady-state plasma concentration of 1-3 IU/mL.

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

Distribution

Bleomycin is rapidly distributed to the tissue, with the highest concentrations accumulating in the skin, lungs, peritoneum and lymph nodes. Low concentrations are found in the bone marrow. Bleomycin is not detectable in the cerebrospinal fluid following intravenous injection. Bleomycin crosses the placental barrier. The apparent volume of distribution (V_d)_B is assumed to be approx. 0.27 +/- 0.09 L/kg. Bleomycin only binds to plasma proteins to a limited extent.

Biotransformation

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

Elimination

The elimination half-life ($T_{1/2\beta}$) is approx. 3 hours after intravenous administration of a bolus injection. Two phases of elimination occur, a brief initial phase ($t_{1/2\alpha}$; 24 min.) followed by a longer terminal phase ($t_{1/2\beta}$; 2–4 hours). After continuous i.v. infusion, the elimination half-life may increase to 9 hours. The systemic plasma clearance (Cl_s) is approximately 1.1 mL/min/kg bw. Approximately 2/3 of the dose administered is excreted unchanged in the urine, probably by glomerular filtration.

After an i.v. or i.m. injection, approximately 50% of the active substance is recovered in the urine. The half-life is considerably prolonged in patients with impaired renal function, to the extent that dose reductions are required. With a creatinine clearance of 35 mL/min, the renal excretion decreases to below 20% with the risk of increased plasma levels. Previous observations indicate that bleomycin is difficult to dialyze.

5.3 Preclinical safety data

Animal experiments have demonstrated teratogenic, mutagenic and carcinogenic properties for bleomycin. Mutagenic effects in humans are expected at clinically relevant exposure levels.

With respect to reproduction toxicity various effects were observed in mice and rats. In rabbits no teratogenicity was observed. In the mouse the female reproductive cells were more sensitive to the cytotoxic and mutagenic effects of bleomycin than the male cells.

Chromosomal abnormalities were observed in human bone marrow cells. The meaning of this for the embryonic/ foetal development in humans is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

6.2 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).

With the exception of the medicinal products specified under section 6.6 (“Special precautions for disposal and other handling”), this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

After reconstitution

Chemical and physical in-use stability of reconstituted and infusion solutions of bleomycin has been demonstrated for 24 hours at 20-25°C and 10 days at refrigerated temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 24 hours at 2°C to 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions of the diluted medicinal product, see section 6.3

6.5 Nature and contents of container

Bleomycin Venus Pharma is a white or cream-colored, lyophilized powder packed in 5 ml tubular (Type I) clear glass vials, stoppered with 20 mm grey butyl rubber stopper and sealed with 20 mm aluminium flip-off seal.

Pack size of 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Safe 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.

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

Instructions for preparation of the solution for injection/infusion:

The entire contents of a vial (15×10^3 IU) should be dissolved in the appropriate quantity of solvent for preparation of the solution. The quantity of IU required for the treatment is then taken from this solution.

Intramuscular injection

Dissolve the contents of a vial in 1-5 mL physiological saline solution. 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.

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.

Intra-arterial infusion

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

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

Intrapleural instillation

Following drainage of the pleural cavity, bleomycin dissolved in 100 mL physiological saline solution, is 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, the patient's position should be changed over 20 minutes at an interval of 5 minutes.

Intratumoural injection

Bleomycin is dissolved in physiological saline solution, producing a concentration of $1-3 \times 10^3$ IU/mL.

7 MARKETING AUTHORISATION HOLDER

Venus Pharma GmbH
Am-Bahnhof 1-3,
59368, Werne,
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 34985/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/10/2023

10 DATE OF REVISION OF THE TEXT

05/10/2023