Induration (with i.m. or local administration)
Rare≥1/10,000 -< 1/1,000
Blood and lymphatic system disorders: Febrileneutropaenia
Cardiac disorders: Myocardial infarction, Pericarditis, Chest pain
Vascular disorder: Cerebral infarction, Thrombotic microangiopathies, Haemolytic uraemic syndrome, Cerebral arteritis, Raynaud' sphenomena, Arterial thrombosis, Deep vein thrombosis
Hepatobiliary disorders: Hepatic impairment
Skin and subcutaneous tissue disorders: Scleroderma
Very Rare <1/10,000:
General disorders and administration site conditions: Tumour lysis syndrome
Not known
Infections and infestations: Sepsis
Blood and lymphatic system disorders: Pancytopenia, Anemia
Vascular disorders: Digitalischemia

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 effect sand 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.

OVERDOSAGE
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.

PHARMACODYANMIC DATA
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.

PHARMACOKINETIC DATA
Absorption
Bleomycin is absorbed to a very limited extent orally. Following intravenous bolus injection of 15 x 10^3 IU/m^2 BSA, peak plasma concentrations of 1-10 IU are reached after approximately 10 minutes. Following i.m. injection of 15 x 10^3 IU, maximum plasma levels of approximately 1 IU are reached after 30 minutes. Continuous infusion of 30 x 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)$_s$ 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 ($T_{½\beta}$) is approx. 3 hours after intravenous administration of a bolus injection. Two phases of elimination occur, a brief initial phase (t1/2α; 24 min.) followed by a longer terminal phase (t1/2β; 2–4 hours). After continuous i.v. infusion, the elimination half-life may increase to 9 hours. The systemic plasma clearance (Cls) 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.

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 sulphydryl groups, terbutaline, or thiols. As bleomycin forms chelating agents with bi- and tervalent cations it should not be mixed with solutions that contain such ions (in particular copper).

STORAGE CONDITIONS
Unopened vials of Bleomycin are stable until the date indicated on the package when stored between 2°C- 8°C., in the original package. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.
Keep out of the reach of children

INSTRUCTION FOR USE AND HANDLING
Administration
Bleomycin for Injection may be given by the intramuscular, intravenous, subcutaneous or intrapleuralroutes.

Administration Precautions
Caution should be exercised when handling Bleomycin for injection. Procedures for proper handling and disposal of anti cancer drugs should be utilized. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing Bleomycin for injection. If Bleomycin for injection contacts the skin, immediately wash the skin thoroughly with soap and water. If contact with mucous membranes occurs, the membranes should be flushed immediately and thoroughly with water.

Intramuscular or Subcutaneous
The Bleomycin for Injection, USP 15 units vial should be reconstituted with 1 to 5 mL of Sterile Water for Injection, USP, Sodium Chloride for Injection, 0.9%, USP, or Sterile Bacteriostatic Water for Injection, USP. The Bleomycin for Injection, USP 30 units vial should be reconstituted with 2 to 10 mL of the above diluents.

Intravenous
The contents of the 15 units or 30 units vial should be dissolved in 5 mL or 10 mL, respectively of Sodium Chloride for Injection, 0.9%, USP, and administered slowly over a period of 10 minutes.

Intrapleural
Sixty units of Bleomycin are dissolved in 50 to 100 mL Sodium Chloride for Injection, 0.9%, USP, and administered through a thoracostomy tube following drainage of excess pleural fluid and confirmation of complete lung expansion. The literature suggests that successful pleurodesis is, in part, dependent upon complete drainage of the pleural fluid and reestablishment of negative intrapleural pressure prior to instillation of a sclerosing agent. Therefore, the amount of drainage from the chest tube should be as minimal as possible prior to instillation of Bleomycin. Although there is no conclusive evidence to support this contention, it is generally accepted that chest tube drainage should be less than 100 mL in a 24-hour period prior to sclerosis. However, Bleomycin instillation may be appropriate when drainage is between 100 to 300 mL under clinical conditions that necessitate sclerosis therapy. The thoracostomy tube is clamped after Bleomcyin instillation. The patient is moved from the supine to the left and right lateral positions several times during the next four hours. The clamp is then removed and suction reestablished. The amount of time the chest tube remains in place following sclerosis is dictated by the clinical situation.
The intrapleural injection of topical anesthetics or systemic narcotic analgesia is generally not required.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior toadministration, whenever solution and container permit.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Potential side effects of the chemotherapy with Bleomycin, e.g. nausea and vomiting may indirectly impair the patient's ability to drive or to use machines

INSCRIPTION IN A LIST OF POISONOUS SUBSTANCE
Not applicable

MA HOLDER AND MANUFACTURER
Getwell Pharmaceuticals
474, Udyog Vihar, Phase-V,
Gurgaon - 122016, Haryana, India

PACKAGING
Flint Glass Vial of 5 ml and 10 ml

Updated on 10/2016

If in doubt do not hesitate to seek advice from your doctor or pharmacist

0700CYGE1015-00

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

BLEOWEL™

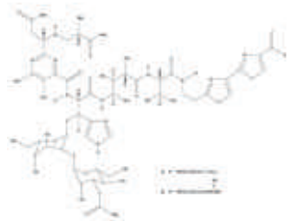
Bleomycin for Injection USP

WARNING

It is strictly recommended that bleomycin be administered under the supervision of a qualified physician experienced in the use of chemotherapeutic agents as it has many adverse reactions, the most severe being pulmonary fibrosis (which initially starts as pneumonitis).
Idiosyncratic reactions which constitute hypotension, mental confusion, fever, chills & wheezing also occur in approximately 1% of lymphoma patients which may be immediate or delayed for several hours & usually occur after the first and second dose and therefore careful monitoring is essential.
Bleomycin is contraindicated in cases of known hypersensitivity to bleomycin, pregnancy and breast-feeding.

DESCRIPTION:
Bleomycin is a cell cycle-phase specific drug from the antibiotic class of antineoplastic drugs. It is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of Streptomyces verticillus. Bleomycin is readily soluble in water.

CHEMICAL STRUCTURE:
Bleomycins are a group of related basic glycopeptides that differ in the terminal amine substituent of common structural unit - bleomycin acid.
Bleomycin A_2 & B_2 are the main components of bleomycin injection. Bleomycin A_2 is chemically N1-[3-(dimethyl sulfonic) propyl)] - bleomycinamide and bleomycin B_2 is chemically N1-[4 - (aminolmnomethyl) amino] butyl] - bleomycin amide.
The molecular weight of bleomycin A_2 is 1414 and that of bleomycin B_2 is 1425. The structural formula for bleomycin is detailed below:



PHARMACEUTICAL FORM, DOSAGE AND ROUTE OF ADMINISTRATION
Pharmaceutical Form: Powder for Injection
Dosage: 15 Units & 30 Units
Route of Administration: IV/IM & Subcutaneous only

QUALITATIVE AND QUANTITATIVE COMPOSITION
BLEOWEL – 15 Units
Each vial contains:
Bleomycin Sulphate USP
Equivalent to Bleomycin 15 Units

BLEOWEL – 30 Units
Each vial contains:
Bleomycin Sulphate USP
Equivalent to Bleomycin 30 Units

EXCIPIENTS WITH KNOWN EFFECTS
Not applicable, as none of Excipients having any pharmacological effects.

THERAPEUTIC INDICATIONS
Bleomycin for Injection should be considered a palliative treatment. It has been shown to be useful in the management of the following neoplasms either as a single agent or in proven combinations with other approved chemotherapeutic agents:
Squamous Cell Carcinoma
Head and neck (including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccalmucosa, gingivae, epiglottis, skin, larynx), penis, cervix, and vulva. The response to bleomycin is poorer in patients with previously irradiated head and neck cancer.
Lymphomas
Hodgkin's disease, non-Hodgkin's lymphoma.
Testicular Carcinoma
Embryonal cell, choriocarcinoma, and teratocarcinoma.
Malignant Pleural Effusion
Bleomycin is effective as a sclerosing agent for the treatment of malignant pleural effusion and prevention of recurrent pleural effusions.

DOSAGE AND ADMINISTRATION
Squamous cell carcinoma, non-Hodgkin's lymphoma, testicular carcinoma: 0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Hodgkin's Disease: 0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, orsubcutaneously weekly or twice weekly. After a 50% response, a maintenance dose of 1 unit daily or 5 units weekly intravenously or intramuscularly should be given.
Pulmonary toxicity of bleomycin appears to be dose-related with a striking increase when the

total dose is over 400 units. Total doses over 400 units should be given with great caution.
Note: When Bleomycin for Injection is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses.
Improvement of Hodgkin's disease and testicular tumors is prompt and noted within 2 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.
Malignant Pleural Effusion—60 units administered as a single dose bolus intrapleural injection.

Use in Patients with Renal Insufficiency
The following dosing reductions are proposed for patients with creatinine clearance (CrCL) values of less than 50 mL/min:

Patient CrCL (mL/min)	Bleomycin for Injection, USP Dose (%)
50 and above	100
40 to 50	70
30 to 40	60
20 to 30	55
10 to 20	45
5 to 10	40

CrCL can be estimated from the individual patient's measured serum creatinine (Scr) values using the Cockcroft and Gault
formula:
Males CrCL ≥ [weight x (140 - Age)]/(72 x Scr)
Females CrCL ≥ 0.85 x [weight x (140 - Age)]/(72 x Scr)
Where CrCL in mL/min/1.73m^2, weight in kg, age in years, and Scr in mg/dL.

Administration
Bleomycin for Injection may be given by the intramuscular, intravenous, subcutaneous or intrapleuralroutes.

Administration Precautions
Caution should be exercised when handling Bleomycin for injection. Procedures for proper handling and disposal of anticancer drugs should be utilized. To minimize the risk of dermal exposure, always wear impervious gloves when handling vials containing Bleomycin for injection. If Bleomycin for injection contacts the skin, immediately wash the skin thoroughly with soap and water. If contact with mucous membranes occurs, the membranes should be flushed immediately and thoroughly with water.

Intramuscular or Subcutaneous
The Bleomycin for Injection, USP 15 units vial should be reconstituted with 1 to 5 mL of Sterile Water for Injection, USP, Sodium Chloride for Injection, 0.9%, USP, or Sterile Bacteriostatic Water for Injection, USP. The Bleomycin for Injection, USP 30 units vial should be reconstituted with 2 to 10 mL of the above diluents.

Intravenous
The contents of the 15 units or 30 units vial should be dissolved in 5 mL or 10 mL, respectively of Sodium Chloride for Injection, 0.9%, USP, and administered slowly over a period of 10 minutes.

Intrapleural
Sixty units of Bleomycin are dissolved in 50 to 100 mL Sodium Chloride for Injection, 0.9%, USP, and administered through a thoracostomy tube following drainage of excess pleural fluid and confirmation of complete lung expansion. The literature suggests that successful pleurodesis is, in part, dependent upon complete drainage of the pleural fluid and reestablishment of negative intrapleural pressure prior to instillation of a sclerosing agent. Therefore, the amount of drainage from the chest tube should be as minimal as possible prior to instillation of Bleomycin. Although there is no conclusive evidence to support this contention, it is generally accepted that chest tube drainage should be less than 100 mL in a 24-hour period prior to sclerosis. However, Bleomycin instillation may be appropriate when drainage is between 100 to 300 mL under clinical conditions that necessitate sclerosis therapy. The thoracostomy tube is clamped after Bleomcyin instillation. The patient is moved from the supine to the left and right lateral positions several times during the next four hours. The clamp is then removed and suction reestablished. The amount of time the chest tube remains in place following sclerosis is dictated by the clinical situation.
The intrapleural injection of topical anesthetics or systemic narcotic analgesia is generally not required.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CONTRAINDICATIONS
Absolute
- Bleomycin for Injection is contraindicated in patients who have demonstrated a hypersensitivity or an idiosyncratic reaction to it.
- Breastfeeding
- Vaccinations with live vaccine should be avoided in patients

Relative
- Pulmonary infection, severely impaired lung function or a history of lung damage caused by bleomycin.
- It is contraindicated in pregnancy especially during first trimester.
- Patients with creatinine clearance values of less than 50 mL/min should be treated with caution and their renal function should be carefully monitored

Use during Pregnancy and Lactation
Pregnancy Category D
Bleomycin can cause fetal harm when administered to a pregnant woman. It has been shown to be teratogenic in rats. Administration of intraperitoneal doses of 1.5 mg/kg/day to rats (about 1.6 times the recommended human dose on a unit/m^2 basis) on days 6 to 15 of gestation caused skeletal malformations, shortened innominate artery and hydroureter. Bleomycin is abortifacient but not teratogenic in rabbits at intravenous doses of 1.2 mg/kg/day (about 2.4 times the recommended human dose on a unit/m^2 basis) given on gestation days 6 to 18.
There have been no studies in pregnant women. If Bleomycin for Injection is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Bleomycin for Injection.

PRECAUTIONS AND WARNINGS
Precautions
General
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.
Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of bleomycin in humans is unknown. A study in F344-type male rats demonstrated an increased incidence of nodular hyperplasia after induced lung carcinogenesis by nitrosamines, followed by treatment with bleomycin. In another study where the drug was administered to rats by subcutaneous injection at 0.35 mg/kg weekly (3.82 units/m^2 weekly or about 30% at the recommended human dose), necropsy findings included dose-related injection site fibrosarcomas as well as various renal tumors. Bleomycin has been shown to be mutagenic both in vitro and in vivo. The effects of bleomycin on fertility have not been studied.

WARNINGS
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. Although the pulmonary toxicity of bleomycin appears to be dose-related upon exceeding a total dose of 400 units (corresponding to approx. 225 units/m^2 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.
Use during Pregnancy and Lactation
Pregnancy Category D
Bleomycin can cause fetal harm when administered to a pregnant woman. It has been shown to be teratogenic in rats. Administration of intraperitoneal doses of 1.5 mg/kg/day to rats (about 1.6 times the recommended human dose on a unit/m^2 basis) on days 6 to 15 of gestation caused skeletal malformations, shortened innominate artery and hydroureter. Bleomycin is abortifacient but not teratogenic in rabbits at intravenous doses of 1.2 mg/kg/day (about 2.4 times the recommended human dose on a unit/m^2 basis) given on gestation days 6 to 18.
There have been no studies in pregnant women. If Bleomycin for Injection is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Bleomycin for Injection.

DRUG 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 O_2 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 phosphophentoin
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 an 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.

PREGNANCY AND LACTATION
Pregnancy
There are insufficient data on the use of bleomycin in pregnant women. Studies in animals have shown reproduction toxicity. 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 three 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.

SIDE EFFECTS
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.
list of adverse reactions
The following undesirable effects can occur during treatment with bleomycin:
Very Common≥1/10
Respiratory, thoracic and mediastinal disorders: Interstitial pneumonitis, Pulmonary fibrosis, Dyspnoea
Gastrointestinal disorders: Anorexia, Weight loss, Nausea, Vomiting, Mucositis, Stomatitis
Skin and subcutaneous tissue disorders: Erythema,
Pruritus, Striae, Blistering, Hyperpigmentation, Tenderness and swelling of the fingertips, Hyperkeratosis, Hair loss
Common≥1/100 -< 1/10Immune system disorders:
Anaphylaxis, Hypersensitivity, Idiosyncratic drug reactions
Nervous system disorders: Dizziness
Respiratory, thoracic and mediastinal disorders:
Acute respiratory distress syndrome(ARDS), Lung failure, Pulmonary embolism
Skin and subcutaneous tissue disorders : Exanthema, Urticaria, Skin reddening, Induration, Oedema, Dermatitis
General disorders and administration site conditions: Fever, Chills, Malaise
Uncommon≥1/1,000 -< 1/100
Blood and lymphatic system disorders:
Myelosuppression,bLeukopaenia,Neutropaenia,Thrombocytopaenia,Haemorrhage
Nervous system disorders: Dizziness
Vascular disorder: Hypotension
Gastro intestinal disorders: Angular stomatitis, Diarrhoea
Skin and subcutaneous tissue disorders: Deformation and discolouration of the nails, Bulla formation at pressure points
Musculoskeletal and connective tissue disorders: Muscle and joint pain
Renal and urinary disorders: Oliguria, Dysuria, Polyuria, Urinary retention
General disorders and administration site conditions: Pain in the tumour area, Phlebitis, Hypertrophy of the vein wall and venous access constriction (with i.v. administration),