SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Bleomedac 15000 IU (Ph. Eur.) = 15 U (USP)/vial, powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 10 ml contains 15000 IU (Ph. Eur.) of bleomycin sulphate.
1 mg of dry weight of the powder is equivalent to at least 1500 IU (Ph. Eur.).

1 U (USP) is equivalent to 1000 IU (Ph. Eur.)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.
Cake of white or yellowish white powder in sealed vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The administration of bleomycin almost always takes place in combination with other cytostatic medicinal products and/or radiation therapy.

Bleomedac is intended for the treatment of:
- Squamous cell carcinoma (SCC) of the head and neck, external genitalia and cervix.
- Hodgkin's lymphoma.
- Non-Hodgkin's lymphoma of intermediate and high malignancy in adults.
- Testis carcinoma (seminoma and non-seminoma).
- Intrapleural therapy of malignant pleural effusion.

4.2 Posology and method of administration

Posology

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 (also see section 2). 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 medicinal 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, intrapleurally, intraperitoneally, intraarterially or subcutaneously. Local injection directly into the tumour may occasionally be indicated.

The dose and intervals between injections are dependent on the indication, the method of administration, age and condition of the patient. It is recommended to adjust the dose to the body surface of the patient.

Squamous cell carcinoma
- Intramuscular or intravenous injection of 10–15 x 10^3 IU/m^2 once or twice a week. Treatment can be continued in the weeks following this or, which is more common, with intervals of 3–4 weeks, up to a total cumulative dose of 400 x 10^3 IU.
- Intravenous infusion of 10–15 x 10^3 IU/m^2 per day for 6–24 hours on 4 to 7 consecutive days every 3 to 4 weeks. The occurrence of stomatitis is the most indicative way to determine the individual tolerance with respect to the maximum dose.

Testis carcinoma
- Intramuscular or intravenous injection of 10–15 x 10^3 IU/m^2 once or twice a week. Treatment can be continued in the weeks following this or, which is more usual, with intervals of 3–4 weeks, up to a total cumulative dose of 400 x 10^3 IU.
- Intravenous infusion of 10–15 x 10^3 IU/m^2 per day for 6–24 hours on 5 to 6 consecutive days every 3 to 4weeks. The occurrence of stomatitis is the most indicative way to determine the individual tolerance with respect to the maximum dose.

Malignant lymphomas (Hodgkin, non-Hodgkin)
- When used alone, the recommended dose is 5–15 x 10^3 IU once to twice a week, up to a total dose of 225 x 10^3 IU.

Due to the increased risk of an anaphylactic reaction in lymphoma patients, treatment should be started with lower doses (for instance 2 x 10^3 IU).
If no acute reactions occur within 4 hours of observation, the normal dosing schedule can be followed.

Intrapleural therapy of malignant pleural effusions
Bleomycin monotherapy as single dose with up to 60 x 10^3 IU intrapleurally. More details can be found in the current literature.

After drainage of the pleural cavity, 60 x 10^3 IU of bleomycin, dissolved in 100 ml sodium chloride 9 mg/ml (0.9%) solution, is infused along the drainage needle or cannula. After the administration the drainage needle or cannula is removed. Administration can be repeated if required.
Approx. 45% of Bleomycin will be absorbed, this has to be considered for the total dose (body surface area, kidney function, lung function).

Combination therapy
Details about the schedules used in specific indications can be found in current literature.

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

When bleomycin is used in combination with radiation therapy the risk of mucosal damage is increased. For this reason it might be necessary to reduce the dose of bleomycin.
Bleomycin is often used as component in multiple chemotherapeutic schedules (for instance with squamous cell carcinoma, testis carcinoma and lymphoma).
The mucosal toxicity of bleomycin should be taken into account in the selection and dosing of products with similar toxicity when these are used in combination schedules.

Elderly
The total dose of bleomycin in elderly patients should be reduced as follows:

Age (in years)	*Total dose (IU)*	*Dose per week (IU)*
≥80	100 x 10^3 IU	15 x 10^3 IU
70–79	150–200 x 10^3 IU	30 x 10^3 IU
60–69	200–300 x 10^3 IU	30–60 x 10^3 IU
<60	400 x 10^3 IU	30–60 x 10^3 IU

Paediatric population
Until more information is available, the administration of bleomycin in children should only take place in exceptional cases and in special centres. The dose should be based on the recommended adult dose and adjusted to the body surface and body weight.

Renal impairment
With impaired renal function, particularly with creatinine clearance <35 ml/min, the elimination of bleomycin is delayed. There are, however, no guidelines for specific dose adjustments in such patients, but the following have been suggested:
Patients with moderate renal failure (GFR 10 to 50 ml/minute) should receive 75 % of the usual dose given at the normal dose interval and patients with severe renal failure (GFR less than 10 ml/minute) should receive 50 % of the usual dose given at the normal dose interval. No dose adjustment is necessary in patients with a GFR greater than 50 ml/minute.

Method of administration

Intramuscular and subcutaneous injection
Dissolve the required dose in a maximum of 5 ml of a suitable diluent, such as sodium chloride 9 mg/ml (0.9%) solution. If pain occurs at the site of the injection a local anaesthetic (1% lidocaine solution) can be added to the solution suitable for injection.

Intravenous administration
Dissolve the required dose in 5–1000 ml sodium chloride 9 mg/ml (0.9%) solution and slowly inject or add to a running infusion.

Intraarterial administration
A slow infusion with sodium chloride 9 mg/ml (0.9%) solution is used.

Intrapleural injection
Dissolve 60 x 10^3 IU in 100 ml sodium chloride 9 mg/ml (0.9%) solution.

Local/intratumoural injections
Bleomycin is dissolved in sodium chloride 9 mg/ml (0.9%) solution to obtain a concentration of 1–3 x 10^3 IU/ml solution.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Acute lung infection or severely reduced lung function.
- Bleomycin-related lung toxicity or reduced lung function which can indicate bleomycin-related lung toxicity.
- Ataxia telangiectasia.
- Breast-feeding.

4.4 Special warnings and precautions for use

In patients who are treated with bleomycin, a regular lung function study, as well as weekly X-rays of the thorax should be performed. This should be done up to 4 weeks after ending the therapy and patients should be kept under clinical review for approximately 8 weeks.
With concomitant radiation therapy of the thorax, a study or an X-ray of the thorax should possibly be done more frequently. A study of the lung function, in particular the measuring of the carbon monoxide diffusion and vital capacity, often makes an early diagnosis of lung toxicity possible.

If unexplained coughing, dyspnoea, basal crepitations or a diffuse reticular image occurs on the X-ray of the thorax, the administration of bleomycin must be discontinued immediately until bleomycin toxicity has been ruled out as a possible cause. The administration of antibiotics and if required, corticosteroids (for instance 100 mg of hydrocortisone intramuscularly in the form of sodium succinate daily for 5 days, followed by 10 mg of prednisolone 2 times daily) is advised.
In case of lung damage as a result of bleomycin, bleomycin should not be administered any more (see section 4.3).

Pulmonary toxicity of bleomycin appears to be dose related with a striking increase when the total dose is over 400 x 10^3 IU. Total doses over 400 x 10^3 IU should be given with great caution.

Although the lung toxicity of bleomycin clearly increases with a total dose of 400 x 10^3 IU, this can also occur with a considerably lower dose, in particular in elderly patients, patients with a reduced hepatic or renal function, pre-existing lung suffering, prior radiation of the lungs, and patients who receive oxygen. In these cases there is a risk factor for lung toxicity.
Lung function tests with 100% oxygen should not be used in patients who have been treated with bleomycin. Lung function tests with 21% oxygen are recommended.

Because of bleomycin's effects on lung tissue, patients who have received the medicinal product are at increased risk of developing pulmonary toxicity when oxygen is administered during surgery. Long exposure to very high concentrations of oxygen is a known cause of lung damage, but after administration of bleomycin, lung damage can occur at oxygen concentrations lower than those usually considered safe. Optimal intraoperative management thus requires the administration of the lowest inspired oxygen fraction (FIO2) compatible with adequate oxygenation (see section 4.5 and 4.8).
Bleomycin should be used with extreme caution in patients with lung cancer as these patients show an increased incidence of pulmonary toxicity.

Bleomycin sensitivity increases in elderly people.
Pulmonary toxicity has also been observed on occasion in young patients receiving low doses.

As 2/3 of the administered dose of bleomycin is excreted unchanged in the urine, the excretion rate is to a high degree affected by the renal function.
Plasma concentrations are strongly elevated when usual doses are administered to patients with renal function disorders.

This medicinal product should not be administered to pregnant patients or women who are breast-feeding. Animal tests have shown that bleomycin, like most cytostatic medicinal products, can have teratogenic and mutagenic characteristics. Therefore both male and female patients should take adequate contraceptive measures up to six months after the discontinuation of the therapy (see section 4.6).

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.

4.5 Interaction with other medicinal products and other forms of interaction

Digoxin
There 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 lose of efficacy of the cytotoxic medicinal product due to increased hepatic metabolism by phenytoin. Concomitant use is not recommended.

Vinca-alkaloids
In patients with a testis carcinoma who are treated with a combination of bleomycin and vinca-alkaloids, a syndrome has been described that resembles Raynaud's phenomenon: ischaemia of peripheral parts of the body, which can lead to necrosis (fingers, toes, nose).

Live vaccines
Vaccination with live vaccines such as the yellow fever vaccine has resulted in severe and fatal infections when used in combination with immunosuppressive chemotherapeutics. This risk is increased in subjects who are already immunosuppressed by their underlying disease. Use an inactivated vaccine where this exists (poliomyelitis).
This combination must not be used.

Nephrotoxic substances, e.g. cisplatin
Renal damage induced by cisplatin can lead to a decreased clearance of bleomycin. Increased pulmonary toxicity, in some cases fatal, has been reported in patients who received bleomycin and cisplatin.

Oxygen
Administration of oxygen during anaesthesia can result in pulmonary fibrosis.
Patients who have been treated with bleomycin are at greater risk of pulmonary toxicity when pure oxygen is administered during an operation. Reduction of the oxygen concentration during the operation and post-operatively is recommended (see section 4.4 and 4.8).

Radiation therapy
Concomitant radiation therapy can increase the risk of the occurrence of pulmonary and dermatological toxicity.
Prior or current radiation therapy of the thorax is an important factor that can increase the incidence and severity of the lung toxicity.

An increased risk of pulmonary toxicity has been described for the concomitant administration of other agents with pulmonary toxicity, e.g carmustine, mitomycin-C, cyclophosphamide and methotrexate.

Ciclosporine, tacrolimus
Excessive immunosuppression with risk of lymphoproliferation exists.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from 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.
Bleomedac should therefore not be used during pregnancy unless the clinical condition of the woman requires treatment with bleomycin, 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. Genetic counselling is also recommended for patients wishing to have children after therapy.

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.

Breast-feeding

It is unknown whether bleomycin/metabolites are excreted in human milk. Bleomedac is contraindicated during breast-feeding (see section 4.3) due to the possibly very harmful effects on the infant.

Fertility

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

4.7 Effects on ability to drive and use machines

Some side effects, such as nausea, vomiting and fatigue can indirectly have an effect on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Like most cytostatic medicinal products bleomycin can cause both an acute and a delayed toxic effect. Acute symptoms: anorexia, fatigue, nausea and fever.

Tabulated list of adverse reactions
Frequencies in this table are defined using the following convention:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

System Organ Class	Frequency and side effect
Infections and infestations	Not known Infection, Sepsis
Blood and lymphatic system disorders	Uncommon Bone marrow toxicity, leukopenia, neutropenia, thrombocytopenia, haemorrhage Rare Febrile neutropenia Not known Pancytopenia, anaemia
Immune system disorders	Common Hypersensitivity, idiosyncratic drug reaction, anaphylactic reaction
Metabolism and nutrition disorders	Very common Decreased appetite

System Organ Class	Frequency and side effect
Nervous system disorders	Not known Paraesthesia, hyperaesthesia
Cardiac disorders	Rare Myocardial infarction, coronary artery disease
Vascular disorders	Rare Vascular injury, cerebral blood flow disorders, cerebral vasculitis, Haemolytic uraemic syndrome, arterial thrombosis Not known Hypotension, deep vein thrombosis, Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	Very common Interstitial pneumonia, pulmonary fibrosis Common Acute respiratory distress syndrome, pulmonary embolism
Gastrointestinal disorders	Very common Nausea, vomiting, mucosal inflammation, stomatitis, mucosal ulceration Uncommon Diarrhoea
Hepatobiliary disorders	Rare Hepatic impairment
Skin and subcutaneous tissue disorders	Very common Flagellate dermatitis, hyperpigmentation, skin hypertrophy, hyperkeratosis, erythema, rash, skin striae, blister, nail disorder, alopecia
Musculoskeletal and connective tissue disorders	Not known Myalgia, pain in extremity, scleroderma
Reproductive system and breast disorders	Not known Spermatozoa abnormal
General disorders and administration site conditions	Very common Local swelling (fingertips and pressure susceptible places) Common Pyrexia Rare After intra-cavity administration: hypotension, hyperpyrexia Very rare Tumour lysis syndrome Not known Injection site pain, infusion site thrombophlebitis
Investigations	Very common Weight decreased

Description of selected adverse reactions

Blood and lymphatic system disorders

Bleomycin does not appear to have any significant bone marrow depressant properties. Mild thrombopenia can occur, which rapidly disappears after the treatment has been finalised. This is a result of an increased use of platelets and cannot be ascribed to a reduced formation of thrombocytes.

Immune system disorders

Severe hypersensitivity/idiosyncratic reactions, similar to clinical anaphylaxis have been observed in approximately 1% of the patients, primarily in patients with lymphoma.

Anaphylactic reactions 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, wheezing and can be fatal. Treatment is symptomatic including volume expansion, pressor agents, antihistamines, and corticosteroids.

Vascular disorders
Hypotensive episodes have been described in patients with Hodgkin's disease, who were treated with high initial doses. Arterial hypotension and venous occlusion can occur.

Damage to the blood vessels (for instance heart infarction, coronary heart disease, blood flow disorders in the brain, inflammation of the blood vessels in the brain, haemolytic uremic syndrome, Raynaud's phenomenon).

Respiratory, thoracic and mediastinal disorders
The most severe side effect is interstitial pneumonia, which can occur during or, in incidental cases, after the ending of the bleomycin treatment. Interstitial pneumonia occurs in approximately 10 % of the patients who receive bleomycin. Pneumonia caused by bleomycin can lead to lung fibrosis in incidental cases and has caused death in approximately 1 % of the patients who received bleomycin. The risk of pulmonary toxicity increases with the cumulative doses. Pulmonary toxicity can already occur with very low cumulative doses in elderly patients, patients who have received radiation of the thorax or who are receiving oxygen.
It has been suggested that patients who received bleomycin pre-operatively, were at a greater risk of developing pulmonary toxicity. A reduction of the administered oxygen concentration during and after the operation is recommended, when an oxygen percentage of more than 21 % is used (see section 4.4 and 4.5).
Vascular changes occur in the lung, which partially affect the elasticity of the vessel wall.
If unexplained coughing, dyspnoea, basal crepitations or a diffuse reticular image occurs on the X-ray of the thorax, any of these symptoms is a reason to discontinue the administration of bleomycin until the bleomycin toxicity has been ruled out as a cause. There is no specific therapy for lung toxicity related to bleomycin. In some cases a favourable effect was described after treatment with corticosteroids.

Gastro-intestinal disorders
The majority of patients (up to 50% of patients) who received complete treatment with bleomycin, developed damage to the mucous membranes or to the skin (see subsection **Skin and subcutaneous tissue disorders** of section 4.8). Ulceration of the mucous membranes may be potentiated when bleomycin is combined with radiation or other medicinal products that are toxic to the mucous membranes.
Gastro-intestinal side effects such as nausea, vomiting, loss of appetite, weight loss and inflammation of the mucous membranes (mucositis, stomatitis) can occur, primarily with high doses. Anti-emetics can be of use. Stomatitis is rarely severe and usually disappears after the completion of the therapy. Loss of appetite and weight loss are common and may continue for a long time after the end of the treatment.

Skin and subcutaneous tissue disorders
The majority of patients (up to 50 % of patients) who received a complete treatment with bleomycin developed damage to the skin or to the mucous membranes (see subsection **Gastro-intestinal disorders** of section 4.8). These side effects usually occur in the second or third week of the treatment and are usually, but not always, reversible.
Flagellate pigmentation is a form of localised skin hyperpigmentation which occurs in 8 to 38 % of patients who receive bleomycin. The laesions are dose related and are revealed as linear hyperpigmentation involving pruritus. Thickening, hyperkeratosis, redness, sensitivity and swelling of the fingertips, erythema and exanthema primarily on the hands and feet, striae, blisters, changing of the nails, swelling at pressure-susceptible places such as the elbows, and hair loss are rarely severe and usually disappear after the completion of the therapy.
Scleroderma has also been reported in patients who received bleomycin.

Reproductive system and breast disorders
During and just after chemotherapy with bleomycin, aneuploid spermatozoa can occur.

General disorders and administration site conditions

Fever can occur 2 to 6 hours after the first injection (see subsection **Immune system disorders** of section 4.8). In case of continuous fever it might be necessary to administer fever-reducing medicinal products. The incidence of fever decreases with following injections.
Infusion-site thrombophlebitis can occur after intravenous application, pain at the site of the injection or in the area of the tumour can occur after intravenous or intra-cavity administration.

If bleomycin is used as part of a multiple chemotherapy dosing schedule, the toxicity of bleomycin should be kept in mind for the selection and dosing of other cytostatic medicinal products with a similar toxicity.
Modifications and dose changes might be required if other cytostatic medicinal products are administered.
Acute reactions with hyperpyrexia and cardio-respiratory collapse have been reported after intravenous injections with doses that were higher than recommended.
Hypotension, hyperpyrexia and medicine-related cases of death have rarely been reported after the intra-cavity administration of bleomycin.

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 the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific antidote. The acute reactions after an overdose consist of hypotension, fever, pulse increase and general symptoms of shock. Treatment is symptomatic with accurate monitoring of the lung function and haematological parameters.
With respiratory complications the patient should be treated with corticosteroids and broad-spectrum antibiotics. Usually the lung reactions to an overdose (fibrosis) are not reversible, unless they are diagnosed at an early stage. Bleomycin cannot be dialysed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other cytostatic antibiotics, ATC code: L01DC 01.

Bleomycin belongs to the cytostatic antibiotics: it is a mixture of structurally related, alkaline, water soluble, glycopeptide antibiotics with a cytostatic effect. The effect of bleomycin rests on intercalation with single and double strands of DNA, resulting in single and double strand ruptures, which inhibit cell division, growth and DNA synthesis. To a lesser degree, bleomycin also affects the RNA and protein synthesis. Cells in the G2 and M phase of the cell cycle are the most sensitive.
The most important factor in the tissue selectivity of bleomycin is the difference in intracellular inactivation. Squamous cells, with their scarce degree of bleomycin hydrolysis, have a high sensitivity to bleomycin. In sensitive tissues, as well as normal neoplastic tissues, chromosome abnormalities like fragmentation, chromatide ruptures and translocations will be produced frequently.

Higher differentiated tumours usually react better than anaplastic ones.

Enzymatic degradation of bleomycin primarily takes place in the plasma, the liver and other organs and to a lesser degree in the skin and lungs.

5.2 Pharmacokinetic properties

Absorption

Bleomycin is administered parenterally. After intrapleural or intraperitoneal administration bleomycin is absorbed systemically. After intrapleural administration approximately 45% is absorbed in the circulation.
The intramuscular injection of 15 x 10^3 IU in humans resulted in maximum plasma concentrations of 1 IU/ml 30 minutes after administration. Intravenous injection of 15 x 10^3 IU/m^2 in humans resulted in a maximum plasma concentration of 1-10 IU/ml.
Continuous infusion of 30 x 10^3 IU of bleomycin per day for 4 to 5 days resulted in a mean steady state plasma concentration of 1 to 3 IU/ml.

Distribution

After parenteral administration bleomycin is distributed primarily across the skin, lungs, kidneys, peritoneum and lymph. Only low concentrations are present in the bone marrow. In the presence of intact meninges, bleomycin is not able to cross the blood-brain barrier. The distribution volume is approximately 17.5 l/m^2. Bleomycin crosses the placenta.

In the plasma, bleomycin is scarcely bound to plasma proteins.

Biotransformation

The biotransformation is not completely known.
Inactivation of bleomycin takes place through enzymatic degradation by means of bleomycin hydrolysis primarily in the plasma, liver and other organs, in a lesser measure in the skin and lungs.

Elimination

After intravenous administration of a bolus injection, clearance is rapid and two phases of elimination occur. A brief initial phase ($t_{1/2\alpha}$; 24 min.) is followed by a longer terminal phase ($t_{1/2\beta}$; 2–4 hours). After an IV bolus injection of 15 x 10^3 IU/m^2 the peak plasma concentration is 1 to 10 µg/ml. After continuous IV infusion the elimination half-life can increase to approximately 9 hours.
About 2/3 of the administered amount of bleomycin is excreted unchanged in the urine. The excretion rate is highly affected by renal function.
Plasma concentrations are strongly elevated when usual doses are administered to patients with renal function disorders.
Bleomycin is not well dialysed.

5.3 Preclinical safety data

Based on its pharmacological properties, bleomycin has mutagenic, carcinogenic and teratogenic effects, which could be demonstrated in respective experimental systems.
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 mice 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

None.

6.2 Incompatibilities

Bleomedac solutions should not be mixed with solutions containing essential amino acids, rivoflavin, ascorbic acid, dexamethasone, aminophylline, furosemide, carindacillin, cefalotin sodium, terbutaline, hydrocortisone, carbenicillin, nafcillin, benzylpenicillin, cefazolin, methotrexate and mitomycin due to the chemical pharmaceutical or physical incompatibilities.
Substances of the sulfhydryl-type (e.g. glutathione) eliminate the effects of bleomycin.
As bleomycin forms chelating agents with bi- and trivalent cations it should not be mixed with solutions that contain such ions (in particular copper).
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

After reconstitution
After reconstitution in the vial, chemical and physical stability has been demonstrated for 24 hours at 2 °C to 8 °C and for 72 hours at 25 °C.

After dilution
After dilution, chemical and physical stability has been demonstrated for 72 hours at 25 °C in glass bottles and polypropylene syringes.

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 normally not be longer than 24 hours at 2 °C to 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C–8 °C).
For storage conditions after reconstitution/dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml colourless type I glass vials, closed with a butyl rubber stopper covered with a cap made of aluminium (inner cap) and polypropylene (outer cap green).

Pack size: 1 or 10 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Destroy the unused portion.

Intravenous injection
Dissolve the contents of a vial in 5–10 ml of sodium chloride 9 mg/ml (0.9%) solution.

Intravenous infusion
Dissolve the contents of a vial in 200–1000 ml of sodium chloride 9 mg/ml (0.9%) solution.

Intramuscular and subcutaneous injection
Dissolve the contents of a bleomycin 15000 vial in 1–5 ml of sodium chloride 9 mg/ml (0.9%) solution. If pain occurs at the site of the injection a local anaesthetic can be added to the solution suitable for injection.

Intraarterial administration
A slow infusion with sodium chloride 9 mg/ml (0.9%) solution is used.

Intrapleural administration
60 x 10^3 IU of bleomycin is dissolved in 100 ml sodium chloride 9 mg/ml (0.9%) solution.

Local/intratumoural injections
Bleomycin is dissolved in sodium chloride 9 mg/ml (0.9%) solution to obtain a concentration of 1 – 3 x 10^3 IU/ml.

Safe handling
The usual caution for the preparation and administration of cytostatic medicinal products is required. For safety information and disposal processing, the guideline with respect to safe handling of antineoplastic medicinal products must be followed.
Specially trained personnel must take care of the preparation. Pregnant women must be warned to avoid handling of cytotoxic agents. The preparation must be done under aseptic circumstances. This should be performed in a designated area. It is forbidden to smoke, eat, or drink in this area. Protective measures consist of the use of gloves, mask, safety goggles, and protective clothing. Use of a laminar airflow (LAF) cabinet is recommended. During the administration, gloves should be worn. Disposal processing procedures must take into account the cytotoxic nature of this substance. Direct contact with the skin, eyes, and mucous membranes must be prevented. In case of direct contact, immediately wash thoroughly with water. For cleaning of the skin, soap can be used. Excreta and vomit must be handled with care.

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 September 2010
Date of latest renewal: 22 September 2015

10. DATE OF REVISION OF THE TEXT

07/2022