IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0437/038/001
Case No: 2045348

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

HOSPIRA UK Ltd

Queensway, **Royal Leamington Spa**, **Warwickshire CV31 3RW**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

BLEOMYCIN 15,000 IU Powder for Injection

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **20/02/2008** until **17/09/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bleomycin 15,000 IU Powder for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains bleomycin 15,000 IU (as bleomycin sulphate).

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection
Vials containing a white to cream coloured powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Squamous cell carcinoma affecting the mouth nasopharynx and paranasal sinuses, larynx, oesophagus, external genitalia, cervix or skin. Well-differentiated tumours usually respond better than anaplastic ones.

2. Hodgkin's disease and other malignant lymphomas including mycosis fungoides.

3. Testicular teratoma.

4. Malignant effusions of serous cavities.

5. Secondary indications in which bleomycin has been shown to be of some value (alone or in combination with other drugs) include metastatic malignant melanoma, carcinoma of the thyroid, lung and bladder.

4.2 Posology and method of administration

Adults

Bleomycin is usually administered intramuscularly but may be given intravenously (bolus or drip), intra-arterially, intrapleurally or intraperitoneally as a solution in physiological saline. Local injection directly into the tumour may occasionally be indicated.

1. *Squamous cell carcinoma and testicular teratoma:*

Used alone the normal dosage is 15 x 10^3 I.U. three times a week or 30 x 10^3 I.U. twice a week, either intramuscularly or intravenously.

Treatment may continue on consecutive weeks, or more usually at intervals of 3-4 weeks, up to a total cumulative dose of 500 x 10^3 I.U. although young men with testicular tumours have frequently tolerated twice this amount. Continuous intravenous infusion at a rate of 15 x 10^3 I.U. per 24 hours for up to 10 days, or 30 x 10^3 I.U. per 24 hours for up to 5 days may produce a therapeutic effect more rapidly. The development of stomatitis is the most useful guide to the determination of individual tolerance of maximum therapeutic response. The dose may need to be adjusted when

bleomycin is used in combination chemotherapy. Use in elderly or children - see below.

2. *Malignant lymphomas:*

Used alone the recommended dosage regimen is 15 x 10^3 I.U. once or twice a week, intramuscularly, to a total dose of 225 x 10^3 I.U. dosage should be reduced in the elderly. The dose may need to be adjusted when bleomycin is used in combination chemotherapy. Use in children - see below.

3. *Malignant effusions:*

After drainage of the affected serous cavity, 60 x 10^3 I.U. bleomycin dissolved in 100 ml physiological saline is introduced via the drainage needle or cannula. After instillation, the drainage needle or cannula may be withdrawn. Administration may be repeated if necessary subject to a total cumulative dose of 500 x 10^3 I.U. Use in elderly or children - see below.

Combination therapy:

Bleomycin is commonly used in conjunction with radiotherapy, particularly in the treatment of cancer of the head and neck region. Such a combination may enhance mucosal reactions if full doses of both forms of treatment are used and bleomycin dosage may require reduction, e.g. to 5 x 10^3 I.U. at the time of each radiotherapy fraction five days a week. Bleomycin is frequently used as one of the drugs in multiple chemotherapy regimens (e.g. in squamous cell carcinoma, testicular teratoma, and lymphoma).

The mucosal toxicity of bleomycin should be borne in mind in the selection and dosage of drugs with similar toxic potential used in such combinations.

Elderly patients:

The total dose of bleomycin used in the treatment of squamous cell carcinoma, testicular teratoma or malignant effusions should be reduced as indicated below.

Age in years	*Total dose (IU)*	*Dose per week (IU)*
80 and over	100 x 10^3	15 x 10^3
70 –79	150 - 200 x 10^3	30 x 10^3
60 – 69	200 - 300 x 10^3	30 - 60 x 10^3
Under 60	500 x 10^3	30 - 60 x 10^3

Children:

Until further data are available, administration of bleomycin to children should take place only under exceptional circumstances and in special centres. The dosage should be based on that recommended for adults and adjusted to body surface area or body weight.

Reduced kidney function:

With serum creatinine values of 177-354 micromol/l (2-4 mg%), half the above individual dosage is recommended. With serum creatinine above 354 micromol/l (4 mg%), a further reduction in dose is indicated.

Preparation of solutions:

For intramuscular injections the required dose is dissolved in up to 5 ml of a suitable solvent such as physiological saline. If pain occurs at the site of injection a 1% solution of lignocaine may be used as a solvent.

For intravenous injections the dose required is dissolved in 5 - 200ml of physiological saline and injected slowly or added to the reservoir of a running intravenous infusion. For intra-arterial administration a slow infusion in physiological saline is used. For intra-cavitary injection 60 x 10^3 I.U. is dissolved in 100 ml normal saline.

For local injections bleomycin is dissolved in physiological saline to make a 1 - 3 x 10^3 I.U./ml solution.

4.3 Contraindications

Bleomcycin is contraindicated in patients with acute pulmonary infection or greatly reducing lung function.

Lung function tests which use 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.

4.4 Special warnings and precautions for use

It is recommended that Bleomycin be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are available. Patients receiving bleomycin must be observed carefully and frequently during and after therapy.

After injection, bleomycin is readily absorbed and distributed in the body, particularly in the skin, lungs and any susceptible tumour tissue, leading to possible skin and pulmonary toxicity, as well as antitumour activity.

Patients undergoing treatment with bleomycin should have chest X-rays weekly. These should continue to be taken for up to four weeks after completion of the course. If breathlessness or infiltrates, not obviously attributable to tumour or to co-existent lung disease, appear, administration of the drug must be stopped immediately and patients should be treated with a corticosteroid (e.g. hydrocortisone 100 mg i.m. as the sodium succinate daily for five days, followed by oral prednisolone 10 mg twice daily) and a broad-spectrum antibiotic.

It has been suggested that sequential measurement of pulmonary diffusion capacity for carbon monoxide (DLco) during bleomycin therapy may be of value in predicting pulmonary toxicity. When used to detect pulmonary toxicity, DLco determinations should be performed monthly and the drug should be discontinued when the DLco is less than 30-35% of the pre-treatment value.

Anaesthesia
Because of bleomycin's effects on lung tissue, patients who have received the drug 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 (FIO_2) compatible with adequate oxygenation.

Pneumonitis
Pneumonitis due to bleomycin has been treated with corticosteroids in an effort to prevent progression to pulmonary fibrosis. Infectious pneumonitis should receive appropriate antibiotic therapy.

Lung cancer
Bleomycin should be used with extreme caution in patients with lung cancer as these patients show an increased incidence of pulmonary toxicity.

Age Related
Patients over 70 years of age should be closely observed for signs of pulmonary toxicity due to bleomycin therapy (See adverse Reactions).

Cumulative dose
Pulmonary toxicity is more common in patients receiving a total dose of more than 400 units (U.S.P.).

Renal or hepatic toxicity
Renal or hepatic toxicity, beginning as deterioration in renal or liver function tests, have been reported infrequently. These toxicities may occur, however, at any time after initiation of therapy.

Idiosyncratic Reactions
Idiosyncratic reactions similar to anaphylaxis have been reported in 1% of lymphoma patients treated with bleomycin. Since these usually occur after the first or second dose, careful monitoring is essential after these doses.

Lymphoma patients
All lymphoma patients should receive test doses of bleomycin before initiating full-dose therapy.

This product should not normally be administered to patients who are pregnant or mothers who are breast-feeding. Animal experiences have revealed that bleomycin, like most cytotoxics, may have teratogenic and carcinogenic potential.

Because of possible skin changes, direct contact of bleomycin with the skin should be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Digoxin - serum levels of Digoxin may be reduced and its actions may be decreased. It is thought that drug-induced alterations of the intestinal mucosa may be involved in the reduced G.I. absorption.

Phenytoin - serum concentrations of phenytoin may be decreased due to decreased absorption or increased metabolism of phenytoin.

Nephrotoxic Agents, e.g. Cisplatin - enhanced pulmonary toxicity, in some cases fatal, has been reported in patients given bleomycin and cisplatin. Concurrent use of renally toxic drugs should therefore be undertaken with caution. Oxygen support during general anaesthesia may result in pulmonary fibrosis. Concurrent radiotherapy may increase the incidence of pulmonary and dermatological toxicities.

4.6 Pregnancy and lactation

Bleomycin has caused, is suspected to have caused or may be expected to cause, an increase incidence of human foetal malformations or irreversible damage. It may also have adverse pharmacological effects.

It is not known whether bleomycin is excreted in breast milk or whether it has a harmful effect on the newborn. Therefore it is not recommended for nursing mothers unless the expected benefits outweigh any potential risks to the newborn.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Like most cytotoxic agents bleomycin can give rise both to immediate and to delayed toxic effects. The most immediate effect is fever on the day of injection. Anorexia, tiredness or nausea may also occur.

Local pain may occur after intravenous or intracavitary injection and other rare effects are hypotension and local thrombophlebitis after intravenous administration.

The majority of patients who receive a full course of bleomycin develop lesions of the skin or oral mucosa. Flagellate pigmentation is a form of localized skin hyperpigmentation that occurs in 8% to 38% of patients receiving bleomycin. The lesions are dose related, and occur as linear hyperpigmentation accompanied by pruritus. Induration,

hyperkeratosis, reddening, tenderness, and swelling of the tips of the fingers, ridging of the nails, bulla formation over pressure points such as elbows, loss of hair and stomatitis are rarely serious and usually disappear soon after completion of the course.

The most serious delayed effect is interstitial pneumonia, which may develop during, or occasionally after, a course of treatment. This condition may sometimes develop into fatal pulmonary fibrosis, although such an occurrence is rare at recommended doses.

Previous or concurrent radiotherapy to the chest is an important factor in increasing the incidence and severity of lung toxicity. It has been suggested that those patients who have received bleomycin preoperatively are at greater a risk of developing pulmonary toxicity, and a reduction in inspired oxygen concentration during the operation and post-operatively is recommended.

Acute fulminant reactions with hyperpyrexia and cardiorespiratory collapse have been reported after intravenous injections of doses higher than those recommended. Hypotension, hyperpyrexia and drug related deaths have been reported rarely following intra-cavitary instillation of bleomycin.

When bleomycin is used as one of the drugs in multiple chemotherapy regimens the toxicity of bleomycin should be borne in mind in the selection and dosage of drugs with similar toxic potential. The addition of other cytotoxic drugs can necessitate changes and dose alterations.

In patients treated for testicular cancer with a combination of bleomycin and vinca alkaloids a syndrome has been reported corresponding to morbus Raynaud, ischaemia which can lead to necrosis of peripheral parts of the body (fingers, toes, nose tip).

4.9 Overdose

No specific antidote. The acute reaction to an overdosage with bleomycin would probably include hypotension, fever, rapid pulse and general symptoms of shock. Treatment is purely symptomatic. In the event of respiratory complications, the patient should be treated with a corticosteroid and a broad-spectrum antibiotic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Although the precise mechanism of action of bleomycin is not fully known, it is thought that the primary action is to produce single and double-stranded breaks in DNA, leading to inhibition of cell division and growth, and inhibition of DNA synthesis in the cells.

Bleomycin is probably most effective against cells in the M and G2 (premitotic) phase of the cell cycle. Bleomycin has not been shown to have an immunosuppressive effect *in vitro*, and shows no significant inhibition of immune response in patients treated with the drug.

Bleomycin - inactivating enzyme has been detected in both normal and malignant cells and is particularly prominent in liver. The enzyme is not found in lung or skin, two normal tissues sensitive to bleomycin action.

5.2 Pharmacokinetic properties

Bleomycin is well absorbed in animals upon intramuscular and subcutaneous administration. Intramuscular injection of 15 units in man resulted in a maximum serum concentration of 1 milliunit/ml 30 minutes after administration. Intravenous injection of 15 units in man resulted in a maximum serum concentration of 3.3 milliunits/ml.

The plasma half-lives have varied from 15-60 minutes in patients with normal renal function following I.V. administration. The serum half-life is prolonged in patients with renal dysfunction. In one patient with severe renal dysfunction the biological half-life was 21 hours when the creatinine clearance was 10.7 ml/min, and 13 hours when

the creatinine clearance was 15.2 ml/min.

There were undetectable serum levels of bleomycin 72 hours after the I.V. dose.

After I.V. injection an average of 40% of the administered dose is recovered unchanged in the urine within 24 hours. After I.M. injection 20% is recovered in the urine after 6 hours. Bleomycin is metabolised by various tissues to some extent Bleomycin will cross the placenta. Equilibrium dialysis and gel permeation experiments suggests that less than 1.0% of the drug is protein-bound after incubation with normal human serum *in vitro*.

The drug concentration is very low in the brain and CSF. In mice bleomycin diffusing from the blood produce high concentrations in the skin, lungs, kidneys, peritoneum lymphatic system and susceptible tumour tissue if present.

5.3 Preclinical safety data

There is no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Bleomycin solutions should not be mixed with solutions of essential amino acids, riboflavin, ascorbic acid, dexamethasone, aminophylline or frusemide, cephalotin sodium, benzylpenicillin sodium, methotrexate, mitomycin, hydrocortisone sodium succinate.

6.3 Shelf Life

As packaged for sale: 2 years.

In use: Chemical and physical in-use stability has been demonstrated for 10 days at 2-8°C when protected from light. 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 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

As packaged for sale: Do not store above 25°C. Keep container in the outer carton.

After reconstitution/dilution: see 6.3.

6.5 Nature and contents of container

10 ml, clear 20mm Type I glass vial, 20mm West Type 1816 rubber closure, aluminium with plastic ‘flip-off’ tops in singles or packs of 10.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Single use only. Discard any unused contents.

Preparation of solutions:
For intramuscular injections the required dose is dissolved in up to 5 ml of a suitable solvent such as physiological saline. If pain occurs at the site of injection a 1% solution of lignocaine may be used as a solvent.

For intravenous injections the dose required is dissolved in 5-200 ml of physiological saline and injected slowly or added to the reservoir of a running intravenous infusion. For intra-arterial administration a slow infusion in physiological saline is used. For intra-cavitary injection 60 x 10^3 I.U. is dissolved in 100 ml normal saline.

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7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire CV31 3RW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 437/38/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 1998

Date of last renewal: 18 September 2003

10 DATE OF REVISION OF THE TEXT

February 2008