IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0361/023/001
Case No: 2045415

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

Martindale Pharmaceuticals Ltd

Bampton Road, **Harold Hill**, **Romford**, **RM3 8UG**, **United Kingdom**

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

Epirubicin Martindale Pharma 2 mg/ml Solution for Injection/Infusion

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 **02/10/2009** until **01/10/2014**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epirubicin Martindale Pharma 2 mg/ml Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of solution for injection/infusion contains 2 mg Epirubicin hydrochloride.

Each 5 ml vial contains a total content of Epirubicin hydrochloride of 10 mg.
Each 10 ml vial contains a total content of Epirubicin hydrochloride of 20 mg.
Each 25 ml vial contains a total content of Epirubicin hydrochloride of 50 mg.
Each 50 ml vial contains a total content of Epirubicin hydrochloride of 100 mg.
Each 100 ml vial contains a total content of Epirubicin hydrochloride of 200 mg.

Excipient: contains sodium 3.54 mg/ml (0.154 mmol)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection/Infusion

A clear red solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Epirubicin is used in the treatment of a range of neoplastic conditions including:
- Carcinoma of the breast
- Advanced ovarian cancer
- Gastric cancer
- Small cell lung cancer

When administered intravesically, epirubicin has been shown to be beneficial in the treatment of:
- Papillary transitional cell carcinoma of the bladder
- Carcinoma-in-situ
- Intravesical prophylaxis of recurrences of superficial bladder carcinoma following transurethral resection.

4.2 Posology and method of administration

Epirubicin is for intravenous or intravesical use only.
The safety and efficacy of epirubicin in children has not been established.

Intravenous administration
It is advisable to administer epirubicin via the tubing of a free-running intravenous saline infusion after checking that the needle is properly placed in the vein. Care should be taken to avoid extravasation (see section 4.4). In case of extravasation, administration should be stopped immediately.

Conventional dose
When epirubicin is used as a single agent, the recommended dosage in adults is 60-90 mg/m^2 body surface area. Epirubicin should be injected intravenously over 3-5 minutes. The dose should be repeated at 21-day intervals, depending upon the patient's haematological status and bone marrow function.

If signs of toxicity, including severe neutropenia/neutropenic fever and thrombocytopenia occur (which could persist at day 21), dose modification or postponement of the subsequent dose may be required.

High dose
Epirubicin as a single agent for the high dose treatment of lung cancer should be administered according to the following regimens:

- Small cell lung cancer (previously untreated): 120 mg/m^2 day 1, every 3 weeks.

For high dose treatment, epirubicin may be given as an intravenous bolus over 3-5 minutes or as an infusion of up to 30 minutes duration.

Breast Cancer
In the adjuvant treatment of early breast cancer patients with positive lymph nodes, intravenous doses of epirubicin ranging from 100 mg/m^2 (as a single dose on day 1) to 120 mg/m^2 (in two divided doses on days 1 and 8) every 3-4 weeks, in combination with intravenous cyclophosphamide and 5-fluorouracil and oral tamoxifen, are recommended.

Lower doses (60-75 mg/m^2 for conventional treatment and 105-120 mg/m^2 for high dose treatment) are recommended for patients whose bone marrow function has been impaired by previous chemotherapy or radiotherapy, by age, or neoplastic bone marrow infiltration. The total dose per cycle may be divided over 2-3 successive days.

The following doses of epirubicin are commonly used in monotherapy and combination chemotherapy for various tumours, as shown:

Cancer Indication	Epirubicin Dose (mg/m^2)[a]	
	Monotherapy	Combination Therapy
Advanced ovarian cancer	60-90	50-100
Gastric cancer	60-90	50
SCLC	120	120
Bladder cancer	50 mg/50 ml or 80 mg/50 ml (carcinoma in situ) Prophylaxiz: 50 mg/50 ml weekly for 4 weeks then monthly for 11 months	

[a] Doses generally given Day 1 or Day 1, 2 and 3 at 21-day intervals

Combination therapy
If epirubicin is used in combination with other cytotoxic products, the dose should be reduced accordingly. Commonly used doses are shown in the table above.

Impaired liver function
The major route of elimination of epirubicin is the hepatobiliary system. In patients with impaired liver function the dose should be reduced based on serum bilirubin levels as follows:

Serum Bilirubin	Dose Reduction
24 - 51 µmol/l	50%
> 51 µmol/l	75%

Impaired renal function
Moderate renal impairment does not appear to require a dose reduction in view of the limited amount of epirubicin excreted by this route. However, dosage adjustment may be necessary in patients with serum creatinine >5 mg/dL.

Intravesical administration
Epirubicin can be given by intravesical administration for the treatment of superficial bladder cancer and carcinoma-in-situ. It should not be given intravesically for the treatment of invasive tumours that have penetrated the bladder wall, systemic therapy or surgery is more appropriate in these situations (see section 4.3). Epirubicin has also been successfully used intravesically as a prophylactic agent after transurethral resection of superficial tumours to prevent recurrence.

For the treatment of superficial bladder cancer the following regimen is recommended, using the dilution table below:
8 weekly instillations of 50 mg/50 ml (diluted with saline or water for injection).
If local toxicity is observed: A dose reduction to 30 mg/50 ml is advised.
Carcinoma-in-situ: Up to 80 mg/50 ml (depending on individual tolerability of the patient)
For prophylaxis: 4 weekly administrations of 50 mg/50 ml followed by 11 monthly instillations at the same dose.

DILUTION TABLE FOR BLADDER INSTILLATION SOLUTIONS

Dose epirubicin required	Volume of 2 mg/ml epirubicin injection	Volume of diluent water for injection or 0.9% sterile saline	Total volume for bladder installation
30 mg	15 ml	35 ml	50 ml
50 mg	25 ml	25 ml	50 ml
80 mg	40 ml	10 ml	50 ml

The solution should be retained intravesically for 1-2 hours. To avoid undue dilution with urine, the patient should be instructed not to drink any fluid in the 12 hours prior to instillation. During the instillation, the patient should be rotated occasionally and should be instructed to void urine at the end of the instillation time.

For instructions on dilution of the product before administration see section 6.6.

4.3 Contraindications

Epirubicin is contraindicated in:

- Patients who have demonstrated hypersensitivity to the active substance or to any of the excipients.
- Patients with marked myelosuppression induced by previous treatment with either other anti-neoplastic agents or radiotherapy.
- Patients treated with maximal cumulative doses of other anthracyclines such as doxorubicin or daunorubicin.
- Patients with current or previous history of cardiac impairment (including 4^{th} degree muscular heart failure, acute heart attack and previous heart attack which led to 3^{rd} and 4^{th} degree muscular heart failure, acute inflammatory heart diseases, arrhythmia with serious haemodynamic consequences).
- Patients with acute systemic infections
- Lactation.

For intravesical administration, epirubicin is contraindicated in:

- Urinary tract infections
- Invasive tumours penetrating the bladder
- Catheterisation problems
- Vesical inflammation
- Large volume of residual urine
- Contracted bladder.

4.4 Special warnings and precautions for use

Epirubicin should only be administered under the supervision of a qualified physician who is experienced in the use of chemotherapeutic agents. Diagnostic and treatment facilities should be readily available for management of therapy and possible complications due to myelosuppression, especially following treatment with higher doses of epirubicin.

Epirubicin can have genotoxic effects. Therefore, male patients treated with epirubicin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because of the possibility of infertility due to therapy with epirubicin.
Women should not become pregnant during treatment with epirubicin. Men and women should use an effective method of contraception during treatment and for six months thereafter.

Extravasation of epirubicin from the vein during injection may cause severe tissue lesions and necrosis. Venous sclerosis may result from injection into small vessels or repeated injections into the same vein.

Careful baseline monitoring of various laboratory parameters and cardiac function should precede initial treatment with epirubicin.

During treatment with epirubicin, red blood cell, white blood cell, neutrophil and platelet counts should be carefully monitored both before and during each cycle of therapy. Leucopenia and neutropenia are usually transient with conventional and high-dose schedules reaching a nadir between the 10^{th} and 14^{th} day, values should return to normal by the 21^{st} day; they are more severe with high dose schedules. Thrombocytopenia (< 100,000 platelets/mm^3) is experienced in very few patients, even following high doses of epirubicin.

Patients must have adequately recovered from severe stomatitis or mucositis before starting treatment with epirubicin.

In establishing the maximal cumulative dose of epirubicin, consideration should be given to any concomitant therapy with potentially cardiotoxic medicinal products. A cumulative dose of 900-1000 mg/m^2 should only be exceeded with extreme caution with both conventional and high doses of epirubicin. Above this level the risk of irreversible congestive heart failure increases greatly. An ECG is recommended before and after each treatment cycle. Alterations in the ECG tracing, such as flattening or inversion of the T-wave, depression of the S-T segment, or the onset of arrhythmias, generally transient and reversible, need not necessarily be taken as indications to discontinue treatment. With cumulative doses <900 mg/m^2, there is evidence that cardiac toxicity rarely occurs. However, cardiac function must be carefully monitored during treatment to minimise the risk of heart failure of the type described for other anthracyclines. In case of cardiac insufficiency, treatment with epirubicin should be discontinued.

Cardiomyopathy induced by anthracyclines is associated with persistent reduction of the QRS voltage, prolongation beyond normal limits of the systolic interval (PEP/LVET) and a reduction of the ejection fraction. Cardiac monitoring of patients receiving epirubicin treatment is highly important and it is advisable to assess cardiac function by non-invasive techniques. Electrocardiogram (ECG) changes may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity. The risk of serious cardiac impairment may be decreased through regular monitoring of left ventricular ejection fraction (LVEF) during the course of treatment with prompt discontinuation of epirubicin at the first sign of impaired function. The preferred method for repeated assessment of cardiac function is evaluation of LVEF measure by multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiac toxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through follow-up. In patients with risk factors, particularly prior anthracycline or anthracenedione use, the monitoring of cardiac function must be particularly strict.

As with other cytotoxic agents, epirubicin may induce hyperuricaemia as a result of rapid lysis of neoplastic cells. Blood uric acid levels should therefore be checked so that this phenomenon may be recognised and properly managed. Hydration, urine alkalinisation and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumor-lysis syndrome.

Heart failure may appear several weeks after discontinuing therapy with epirubicin and may be unresponsive to specific medical treatment. The potential risk of cardiotoxicity may increase in patients who have received concomitant, or prior, radiotherapy to the mediastinal pericardial area and/or who are under medical treatment with potentially cardiotoxic medicinal products (see section 4.5).

Before commencing therapy with epirubicin, and if possible during treatment, liver function should be evaluated (SGOT, SGT, alkaline phosphatase, bilirubin), (see section 4.2)

Epirubicin may impart a red colour to the urine for one or two days after administration.

4.5 Interaction with other medicinal products and other forms of interaction

It is not recommended that Epirubicin hydrochloride be mixed with other medicinal products. However, epirubicin can be used in combination with other anti-cancer agents.

Drug interactions with epirubicin have been observed with cimetidine, dexverapamil, dexrazoxane, docetaxel, interferon α_{2b}, paclitaxel and quinine.

Dexverapamil may alter the pharmacokinetics of epirubicin and possibly increase its bone marrow depressant effects.

Prior administration of higher doses (900 mg/m^2 and 1200 mg/m^2) of dexrazoxane may increase the systemic clearance of epirubicin and result in a decrease in AUC.

One study found that docetaxel may increase the plasma concentrations of epirubicin metabolites when administered immediately after epirubicin.

The co-administration of interferon α_{2b} may cause a reduction in both the terminal elimination half-life and the total clearance of epirubicin.

Paclitaxel may affect the pharmacokinetics of epirubicin and its metabolite, epirubicinol. In one study, haematological toxicity was greater when paclitaxel was administered before epirubicin compared with after epirubicin.
One study has shown that paclitaxel clearance is reduced by epirubicin.

Quinine may accelerate the initial distribution of epirubicin from blood into the tissues and may have an influence on the red blood cells partitioning of epirubicin.

Cimetidine 400 mg b.i.d given prior to epirubicin 100 mg/m^2 every 3 weeks led to a 50% increase in epirubicin AUC and a 41% increase in epirubicinol AUC (latter $p<0.05$). The AUC of the 7-deoxy-doxorubicinol aglycone and liver blood flow were not reduced, so results are not explained by reduced cytochrome P-450 activity.

Epirubicin used in combination with other cytotoxic agents may result in additive myelotoxicity.

The possibility of a marked disturbance of haematopoiesis needs to be kept in mind with a (pre-) treatment with medications which influence the bone marrow (i.e. cytostatic agents, sulphonamide, chloramphenicol, diphenylhydantoin, amidopyrine-derivate, antiretroviral agents).

The potential risk of cardiotoxicity may increase in patients who have received concomitant cardiotoxic agents (e.g. 5-fluorouracil, cyclophosphamide, cisplatin, taxanes), or concomitant (or prior) radiotherapy to the mediastinal area.

If epirubicin is used concomitantly with other medicinal products that may cause heart failure, e.g. calcium channel blockers, then cardiac function must be monitored throughout the course of treatment.

Epirubicin is mainly metabolised in the liver; each concomitant medication which affects hepatic function can also affect the metabolisation or the pharmacokinetics of epirubicin and, consequently, its efficacy and/or toxicity.

This product is generally not recommended in combination with live attenuated vaccines.

4.6 Pregnancy and lactation

There is no conclusive information as to whether epirubicin may adversely affect human fertility or cause teratogenesis. Experimental data, however, suggest that epirubicin may harm the foetus. Like most other anti-cancer agents, epirubicin has shown mutagenic and carcinogenic properties in animals. Both men and women receiving epirubicin should be informed of the potential risk of adverse effects on reproduction. Women of childbearing potential should be fully informed of the potential hazard to the foetus and the possibility of genetic counselling should be considered if they become pregnant during epirubicin therapy. In cancer chemotherapy, epirubicin should not be used in pregnant women or women of childbearing potential who might become pregnant unless the potential benefits to the mother outweigh the possible risks to the foetus.
Breastfeeding must be discontinued before and during therapy with epirubicin.

4.7 Effects on ability to drive and use machines

There have been no reports of particular adverse events relating to the effects on ability to drive and to use machines.

Epirubicin may cause episodes of nausea and vomiting, which can temporarily lead to an impairment of ability to drive or operate machines.

4.8 Undesirable effects

The estimation of frequency: Very common (≥1/10); common (≥1/100,<1/10); uncommon (≥1/1,000,<1/100); rare (≥ 1/10,000,<1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Investigations
Rare: Increased transaminase levels.

Cardiac disorders
Rare: Cardiotoxicity (ECG changes, tachycardia, arrhythmia, cardiomyopathy, congestive heart failure (dyspnoea, oedema, enlargement of the liver, ascites, pulmonary oedema, pleural effusion, gallop rhythm), ventricular tachycardia, bradycardia, AV block, bundle-branch block) (see section 4.4).

Blood and lymphatic system disorder
Frequency unknown: Myelosuppression (leukopenia, granulcytopenia, neutropenia, febril neutropenia, thrombocytopenia, anaemia), Hemorrhagia and tissue hypoxia (as a result of myelosuppression) may occur. High doses of epirubicin have been safely administered in a large number of untreated patients having various solid tumours and have caused adverse events which are no different from those seen at conventional doses with the exception of reversible severe neutropenia (<500 neutrophils/mm^3 for < 7 days) which occurred in the majority of patients. Only few patients required hospitalisation and supportive therapy for severe infectious complications at high doses.

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea, which can result in dehydration, loss of appetite and abdominal pain. Oesophagitis and hyperpigmentation of the oral mucosa may also occur.

Skin and subcutaneous tissue disorders
Very common: Alopecia, normally reversible, appears in 60-90% of treated cases; it is accompanied by lack of beard growth in males.
Common: Hot flushes.
Uncommon: Hyperpigmentation of skin and nails. Skin reddening.
Rare: Urticaria.

Metabolism and nutrition disorders
Rare: Hyperuricaemia (as a result of rapid lysis of neoplastic cells).

Infections and infestations
Frequency unknown: Fever, infections, pneumonia, sepsis and septic shock may occur as a result of myelosuppression.

Injury, poisoning and procedural complications
Common: Chemical cystitis, in some cases haemorrhagic, is observed following intravesical administration.

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Rare: Secondary acute myeloid leukaemia with or without a pre-leukaemic phase in patients treated with epirubicin in combination with DNA-damaging antineoplastic agents. These leukaemia's have short (1-3 years) latency.

Vascular disorders
Uncommon: Thrombophlebitis.
Frequency unknown: Coincidental cases of thromboembolic events (including pulmonary embolism (in isolated cases with fatal outcome)) have occurred.

General disorders and administration site conditions
Common: Mucositis, may appear 5-10 days after the start of treatment and usually involves stomatitis with areas of painful erosions, ulceration and bleedings, mainly along the side of the tongue and the sublingual mucosa. Redness along the infusion vein. Local phlebitis, phlebosclerosis, Local pain and tissue necrosis may occur (following accidental paravenous injection).
Uncommon: Headache.
Rare: Fever, chills, dizziness, hyperpyrexia, malaise, weakness.

Immune system disorders
Common: Allergic reactions after intravesical administration.
Uncommon: Photosensitivity or hypersensitivity in case of radiotherapy ("recall phenomenon").
Rare: Anaphylaxis (anaphylaxis/anaphylactoid reactions with or without shock including skin rash, pruritus, fever and chills).

Reproductive system and breast disorders
Rare: Amenorrhea, azoospermi.

4.9 Overdose

Very high single doses of epirubicin may be expected to cause acute myocardial degeneration within 24 hours and severe myelosuppression within 10-14 days. Treatment should aim to support the patient during this period and should utilise such measures as antibiotics, blood transfusion and reverse barrier nursing. Delayed cardiac failure has been seen with the anthracyclines up to 6 months after the overdose. Patients should be observed carefully and should, if signs of cardiac failure arise, be treated along conventional lines. Epirubicin is not dialyzable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent. ATC code: L01D B03
Epirubicin is a cytotoxic active antibiotic from the anthracycline group.
The mechanism of action of epirubicin is related to its ability to bind to DNA. Cell culture studies have shown rapid cell penetration, localisation in the nucleus and inhibition of nucleic acid synthesis and mitosis. Epirubicin has proved to be active on a wide spectrum of experimental tumours including L1210 and P388 leukaemias, sarcomas SA180 (solid and ascitic forms), B16 melanoma, mammary carcinoma, Lewis lung carcinoma and colon carcinoma 38. It has also shown activity against human tumours transplanted into athymic nude mice (melanoma, mammary, lung, prostatic and ovarian carcinomas).

5.2 Pharmacokinetic properties

In patients with normal hepatic and renal function, plasma levels after intravenous injection of 60-150 mg/m^2 of the medicinal product follow a tri-exponential decreasing pattern with a very fast first phase and a slow terminal phase with a mean half-life of about 40 hours. These doses are within the limits of pharmacokinetic linearity both in terms of plasma clearance values and metabolic pathway. Between 60 and 120 mg/m^2 there is an extensive linear pharmacokinetic, 150 mg/m^2 is at the margin of dose linearity. The major metabolites that have been identified are epirubicinol (13-OH epirubicin) and glucuronides of epirubicin and epirubicinol.

In pharmacokinetic studies of patients with carcinoma in situ of the bladder the plasma levels of epirubicin after intravesical instillation are typically low (<10 ng/ml). A significant systemic resorption can therefore not be assumed. In patients with lesions of the mucosa of the bladder (e.g. tumour, cystitis, operations), a higher resorption rate can be expected.

The 4'-O-glucuronidation distinguishes epirubicin from doxorubicin and may account for the faster elimination of epirubicin and its reduced toxicity. Plasma levels of the main metabolite, the 13-OH derivative (epirubicinol) are consistently lower and virtually parallel those of the unchanged active substance.

Epirubicin is eliminated mainly through the liver; high plasma clearance values (0.9 l/min) indicate that this slow elimination is due to extensive tissue distribution. Urinary excretion accounts for approximately 9-10% of the administered dose in 48 hours.
Biliary excretion represents the major route of elimination, about 40% of the administered dose being recovered in the bile in 72 hours. The active substance does not cross the blood brain barrier.

5.3 Preclinical safety data

Following repeated dosing with epirubicin, the target organs in rat, rabbit and dog were the haemolymphopoietic system, GI tract, kidney, liver and reproductive organs. Epirubicin was also cardiotoxic in the rat, rabbit and dog.

Epirubicin, like other anthracyclines, was mutagenic, genotoxic, embryotoxic and carcinogenic in rats.

No malformations were seen in rats or rabbits, but like other anthracyclines and cytotoxic active substances, epirubicin must be considered potentially teratogenic.
A local tolerance study in rats and mice showed extravasation of epirubicin causes tissue necrosis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Hydrochloric acid (for pH-adjustment)
Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf Life

Before first opening: 2 years
In use:
Epirubicin hydrochloride may be further diluted, under aseptic conditions, in Glucose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. The infusion solution is chemically and physically stable for up to 24 hours, when prepared under full aseptically controlled conditions in polypropylene syringes and in PVC infusion bags at 2 to 8ºC.

However from a microbiological point of view, it is recommended that 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 to 8ºC.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
For storage conditions after first opening of the vial and of the diluted medicinal product, see section 6.3.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Epirubicin hydrochloride is supplied in clear glass vials (Type I PhEur) with fluoropolymer coated chlorobutyl rubber stoppers (PhEur).

Pack sizes:
1 x 5 ml vial (10 mg/5 ml)
1 x 10 ml vial (20 mg/10 ml)
1 x 25 ml vial (50 mg/25 ml)
1 x 50 ml vial (100 mg/50 ml)
1 x 100 ml vial (200 mg/100 ml)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Epirubicin hydrochloride may be further diluted in Glucose 5% or Sodium Chloride 0.9% and administered as an intravenous infusion. For information on the stability of the infusion solutions please refer to section 6.3.

The injection solution contains no preservative and any unused portion of the vial should be discarded immediately.

Guidelines for the safe handling and disposal of antineoplastic agents:

1. If an infusion solution is to be prepared, this should be performed by trained personnel under aseptic conditions.
2. Preparation of an infusion solution should be performed in a designated aseptic area.
3. Adequate protective disposable gloves, goggles, gown and mask should be worn.
4. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In the event of contact with the eyes, irrigate with large amounts of water and/or 0.9% sodium chloride solution. Then seek medical evaluation by a physician.
5. In case of skin contact, thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush. Always wash hands after removing gloves.
6. Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water. All cleaning materials should be disposed of as detailed below.
7. Pregnant staff should not handle the cytotoxic preparation.

8. Adequate care and precautions should be taken in the disposal of items (syringes, needles etc) used to reconstitute and/or dilute cytotoxic medicinal products. Any unused 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

PA 361/23/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation; 2nd October 2009

10 DATE OF REVISION OF THE TEXT