Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxorubicin Hydrochloride 50 mg Powder for Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxorubicin hydrochloride 50.0 mg per vial.

Excipient: Lactose monohydrate 263.1 mg

When reconsituted as recommended in section 6.6 each ml contains 2 mg doxorubicin hydrochloride.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection.

Orange-red, sterile, freeze-dried powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Doxorubicin has been used successfully in the treatment of neoplastic conditions such as acute leukaemia, soft tissue and osteogenic sarcomas, breast carcinoma, lymphomas, bronchogenic (lung) carcinoma. It has also been used in the treatment of paediatric malignancy. Doxorubicin is frequently used in combination chemotherapy regimen involving other cytotoxic drugs. Doxorubicin can be used in the treatment of non-metastatic transitional cell carcinoma, carcinoma in situ and papillary tumours of the bladder, by intravesical administration.

4.2 Posology and method of administration

Intravenous administration

When used as a single agent, the recommended dosage schedule is 60- 75 mg/m² body surface area, as a single intravenous injection administered at 21 day intervals. If it is used in combination with other antitumour agents having overlapping toxicity, the dosage for doxorubicin may need to be reduced to 30-40 mg/m² every three weeks. If using body weight to calculate the dose, then dosages of 1.2 - 2.4 mg/kg as a single dose every three weeks are recommended.

It has been shown that giving doxorubicin as a single dose every three weeks greatly reduces the distressing toxic effect, mucositis. However, there are some regimens which divide the dose over three successive days (20-25 mg/m² or 0.4-0.8 mg/kg). It is thought that this regimen has greater effectiveness although at a cost of higher toxicity.

Administration of doxorubicin in a weekly regimen has been shown to be as effective as the three weekly regimen. The recommended dosage is 20 mg/m^2 once a week although objective responses have been seen at 6-12 mg/m^2. This regimen of weekly dosing also reduces the incidence of cardiotoxicity.

It is particularly important to reduce the dose of doxorubicin if it is used in combination with other drugs with a similar toxicity profile. The recommended lifetime cumulative dose limit is 450-550 mg doxorubicin hydrochloride/m^2 body surface area.

It is recommended that doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection 0.9% or 5% Glucose Intravenous Infusion. The tubing should be attached to a Butterfly needle inserted preferably into a large vein. The rate of administration is dependent on the size of the vein and the dosage. However the dose should be administered in not less than 3 to 5 minutes. This technique minimises the risk of thrombosis or perivenous extravasation which can lead to severe cellulitis and vesication.

Intravenous infusion is not advised due to the tissue damage that may occur if the infusion infiltrates the tissues. If a central vein catheter is used then infusion of Doxorubicin in Sodium Chloride 0.9% Injection is advised.

Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Doxorubicin should not be mixed with heparin since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Until specific compatibility data are available, it is not recommended that doxorubicin be mixed with other drugs.

Intravesical administration

This technique may be used for the treatment of transitional cell carcinoma, papillary bladder tumours and carcinoma in situ. It should not be used for invasive tumours of the bladder which have penetrated the bladder wall.

Many regimes are in use, making interpretation difficult, but the following procedure may be a helpful guide:

1. Patient should be instructed not to drink any fluid in the 12 hours prior to the examination.

2. Dissolve 50 mg of doxorubicin in 50 ml of normal saline and instil via the catheter into the bladder.

3. The catheter should be removed and the patient instructed to be on one side. At 15 minute intervals the patient should make a quarter turn over a 1 hour period. At the end of this period, the patient may void.

4. The procedure may be repeated at monthly intervals.

Intra-arterial administration

Doxorubicin Hydrochloride has been administered as an intra-arterial infusion in an attempt to produce local intense activity and reduce systematic toxicity. However it must be recognised that this route of administration is potentially extremely hazardous and can lead to widespread necrosis of perfused tissue unless careful precautions are taken. Intra-arterial administration should be undertaken only by experienced professionals.

Paediatric:

Adult dosage regimes may be suitable for paediatric cases, but may need to be reduced.

Geriatric:

It is recommended that the total cumulative dose of doxorubicin for adult's aged 70 or older be restricted to 450 mg/m^2 body surface area. Adult doses may be suitable for geriatric patients, but may need to be reduced.

Impaired Hepatic Function:

Doxorubicin is metabolised by the liver and excreted in bile. Impairment of liver function results in slower excretion of the drug and consequently increased retention and accumulation in the plasma and tissues, resulting in enhanced clinical toxicity.

Doxorubicin dosage must be reduced if hepatic function is impaired according to the following table:

Serum Bilirubin Levels	BSP Retention	Recommended Dose
20 – 50 micromol/L	9-15%	50% normal dose
Over 50 micromol/L	Over 15%	25% normal dose

Impaired Renal Function:

Doxorubicin and metabolites are excreted in the urine to a minor degree and there are no clear indications that the pharmacokinetics or toxicity of doxorubicin are altered in patients with impaired renal function.

4.3 Contraindications

Hypersensitivity to any of the excipients listed in section 6.1.

Dosage should not be repeated in cases of bone marrow depression or buccal ulceration or buccal burning sensation, which can precede ulceration.

4.4 Special warnings and precautions for use

Experienced Physician: Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. Initial treatment with doxorubicin requires close observation of the patient and extensive laboratory monitoring. It is strongly recommended therefore, that patients be hospitalised at least during the first phase of treatment.

Before or during treatment with doxorubicin, the following monitoring examinations are recommended:

- Radiographs of the lungs and chest, and ECG
- Regular monitoring of heart function (left ventricular ejection fraction [LVEF] by e.g. ECG, echocardiography and multi-gated acquisition [MUGA] scan)
- Daily inspection of the oral cavity and pharynx for mucosal changes
- Blood test: haematocrit, platelets, differential white cell count, AST, ALT, LDH, bilirubin, uric acid

Cardiac Toxicity: Special attention must be given to the cardiac toxicity exhibited by doxorubicin.

Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These symptoms generally indicate acute transient toxicity. Flattening and widening of the QRS-complex beyond normal limits may indicate doxorubicin hydrochloride-induced cardiomyopathy. If this occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

Delayed cardiotoxicity usually develops late in the course of therapy with doxorubicin or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment, have also been reported. For this reason, extreme care should be taken in patients with existing associated heart disease.

Delayed cardiomyopathy is manifested by reduced LVEF and/or signs and symptoms of congestive heart failure (CHF). Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the medicinal product. Severe cardiac failure may occur suddenly, without premonitory ECG changes.

Cardiac function should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy to minimise the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function. A baseline cardiac evaluation with an ECG and either a MUGA scan or an echocardiogram is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or echocardiographic determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses.

It is recommended that the cumulative total lifetime dose of doxorubicin (including related drugs such as daunorubicin) should not exceed 450-550 mg/m^2 body surface area. Above this dosage, the risk of irreversible congestive cardiac failure increases greatly. If the patient has other potential risk factors of cardiotoxicity (history of cardiovascular disease, previous therapy with other anthracyclines or anthracenediones, prior or concomitant radiotherapy to the mediastinal/pericardial area, and concomitant use of medicinal products with the ability to suppress cardiac contractility, including cyclophosphamide and 5-fluorouracil), cardiotoxicity with doxorubicin may occur at lower cumulative does and cardiac function should be carefully monitored.

Bone Marrow Depression: There is a high incidence of bone marrow depression, primarily of leucocytes, requiring careful haematological monitoring. With the recommended dosage schedule, leucopenia is usually transient, reaching its nadir at 10 – 14 days after treatment, with recovery usually occurring by the 21st day.

White blood cell counts as low as 1000/mm^3 are to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored, since they may also be depressed.

Haematological toxicity may require dose reduction or suspension or delay of doxorubicin therapy.

Dosage should not be repeated in the presence or development of bone marrow depression or buccal ulceration. The latter may be preceded by premonitory buccal burning sensations and repetition in the presence of this symptom is not advised. (See Section 4.3, Contraindications).

Immunosuppression: Doxorubicin is a powerful but temporary immunosuppressant agent. Appropriate measures should be taken to prevent secondary infection.

Severe Myelosuppression: Persistent severe myelosuppression may result in superinfection or haemorrhage.

Enhanced Toxicity: It has been reported that doxorubicin may enhance the severity of the toxicity of anticancer therapies, such as cyclophosphamide induced haemorrhagic cystitis, mucositis induced by radiotherapy and hepatotoxicity of 6-mercaptopurine and the toxicity of streptozocin or methotrexate.

Hepatic Impairment: Toxicity to recommended doses of doxorubicin is enhanced by hepatic impairment. It is recommended that an evaluation of hepatic function be carried out prior to individual dosing, using conventional clinical laboratory tests such as AST, ALT, alkaline phosphatase, bilirubin and BSP. If required, dosage schedules should be reduced accordingly (See Section 4.2, Posology and method of administration).

Extravasation: On intravenous administration of doxorubicin, a stinging or burning sensation signifies extravasation and, even if blood return from aspiration of the infusion needle is good, the injection or infusion should be immediately terminated and restarted in another vein.

Should extravasation occur, stop the infusion immediately and apply ice packs to the injection site. Local injection of dexamethasone or hydrocortisone may be used to minimise local tissue necrosis.

Hydrocortisone cream 1% may also be applied locally.

Intravescial administration

Intravesical administration of doxorubicin may cause symptoms of chemical cystitis (i.e. dysuria, urinary frequency, nocturia, stranguria, haematuria, necrosis of the bladder wall). Special attention is needed in case of catheter problems (i.e. urethral obstruction caused by invasion of intravesical tumour). The intravesical route of administration should not be attempted in patients with invasive tumours that have penetrated the bladder wall (beyond T1), urinary tract infections and inflammatory conditions of the bladder.

Urine cytologies and blood counts should be monitored monthly, and cystoscopic examinations should be performed at regular intervals.

Radiotherapy

Special caution is mandatory for patients who have had radiotherapy previously, are having radiotherapy concurrently or are planning to have radiotherapy. These patients are at special risk of local reactions in the radiation field (recall phenomenon) if doxorubicin hydrochloride is used. Severe, sometimes fatal, hepatotoxicity (liver damage) has been reported in this connection. Prior radiation to the mediastinum increases the cardiotoxicity of doxorubicin. The cumulative dose of 400 mg/m^2 must not be exceeded especially in this case.

Vaccines

This medicinal product is generally not recommended in combination with live, attenuated vaccines. Contact to persons recently vaccinated against polio should be avoided.

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin, may result in serious or fatal infections.

Tumour lysis syndrome

Doxorubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells (tumour lysis syndrome). Blood uric acid levels, potassium, calcium phosphate and creatinine should be evaluated after initial treatment. Hydration, urine alkalinisation and prophylaxis with allopurinol to prevent hyperuricaemia may minimise potential complications of tumour lysis syndrome.

4.5 Interaction with other medicinal products and other forms of interaction

Doxorubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines or anthracenediones, or other potentially cardiotoxic drugs (e.g. 5-fluorouracil, cyclophosphamide or paclitaxel) or with products affecting cardiac function (like calcium antagonists). When doxorubicin is used together with these agents, cardiac function must be followed carefully.

Paclitaxel administered shortly before doxorubicin may decrease clearance and increase plasma concentrations of doxorubicin.

The use of trastuzumab in combination with anthracyclines (such as doxorubicin) is associated with a high cardiotoxic risk. Caution should be exercised in patients with impaired cardiac function. The cardiac function of the patients treated concomitantly with doxorubicin and trastuzumab must be appropriately monitored as recommended.

Doxorubicin undergoes metabolism via Cytochrome P450 (CYP450) and is a substrate for the P-glycoprotein (Pgp) transporter. Concomitant administration of inhibitors of CYP450 and/or Pgp might lead to increased plasma concentrations of doxorubicin and thereby increased toxicity.

Conversely, concomitant administration of inducers of CYP450, such as rifampicin and barbiturates, might decrease plasma concentrations of doxorubicin and reduce efficacy.

Ciclosporin, an inhibitor of CYP3A4 and Pgp, increased the AUC of doxorubicin and doxorubicinol. The combination might require dose adjustment. Patients taking concurrent doxorubicin and ciclosporin should be carefully monitored. Cimetidine has also been shown to reduce the plasma clearance and increase the AUC of doxorubicin.

While barbiturates may lead to an accelerated plasma clearance of doxorubicin, the concomitant administration of phenytoin may result in lower plasma phenytoin levels.

Elevated serum doxorubicin concentrations were reported after the concomitant administration of doxorubicin and ritonavir.

The toxic effects of doxorubicin therapy may be increased in combination with other cytostatics (e.g. cytarabine, cisplatin and cyclophosphamide). Necrosis of the large intestine with massive hemorrhage and severe infections may occur in connection with combination therapies with cytarabine.

Clozapine may increase the risk and severity of the haematological toxicity of doxorubicin.

Marked nephrotoxicity of amphotericin B can occur during doxorubicin therapy.

As doxorubicin is rapidly metabolized and predominantly eliminated by the biliary system, the concomitant administration of known hepatotoxic chemotherapeutic agents (e.g. mercaptopurine, methotrexate, streptozocin) could potentially increase the toxicity of doxorubicin as a result of reduced hepatic clearance of the drug. Dosing of doxorubicin must be modified if concomitant therapy with hepatotoxic drugs is mandatory.

Doxorubicin is a potent, radiosensitizing agent (“radiosensitizer”), and recall phenomena induced by it may be life-threatening. Any preceding, concomitant or subsequent radiation therapy may increase the cardiotoxicity or hepatotoxicity of doxorubicin.

Doxorubicin therapy may lead to increased serum uric acid, therefore dose adjustment of uric acid lowering agents may be necessary.

Doxorubicin may reduce oral bioavailability of digoxin.

4.6 Fertility, pregnancy and lactation

Pregnancy

The drug is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits, and trace amounts of the drug have been found in mouse foetuses and in one aborted human foetus. Although there is no conclusive evidence, there is data which suggests that doxorubicin may harm the foetus. It is therefore recommended that doxorubicin is not administered to women who are pregnant.

Breastfeeding

Doxorubicin is distributed into milk. Experimental data suggests that doxorubicin may harm the infant and should therefore not be administered to mothers who are breast feeding.

Fertility

Doxorubicin can have genotoxic effects. Doxorubicin may cause infertility during the time of drug administration. In women, doxorubicin may cause amenorrhoea. Although ovulation and menstruation appear to return after termination of therapy, premature menopause can occur.

Women should not become pregnant during and up to 6 months after treatment.

Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing doxorubicin treatment should use effective contraceptive measures. They are also advised not to father a child during and up to 6 months after treatment and to seek advice on cryopreservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with doxorubicin.

4.7 Effects on ability to drive and use machines

Doxorubicin has moderate influence on the ability to drive and use machines.
Due to the frequent occurrence of drowsiness, nausea and vomiting, driving cars and operation of machinery should be discouraged.

4.8 Undesirable effects

The following adverse events (not listed in order of frequency) have been reported in association with doxorubicin therapy:

Neoplasms Benign and Malignant (including cysts and polyps):
The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported rarely in patients concurrently treated with doxorubicin in association with DNA-damaging antineoplastic agents. Such cases could have a short (1-3 year) latency period. Acute lymphocytic leukaemia and acute myelogenous leukaemia.

Blood and Lymphatic System Disorders:
Haematological monitoring should be undertaken regularly in both haematological and non haematological conditions, because of the possibility of bone-marrow depression (myelosuppression) which may become evident around ten days from the time of administration. Clinical consequences of doxorubicin bone marrow/haematological toxicity may be fever, infections, sepsis/septicaemia, septic shock, haemorrhages, tissue hypoxia or death. Leucopenia, neutropenia, anaemia and thrombocytopenia.

Myelosuppression is more common in patients who have had extensive radiotherapy, bone infiltration by tumour, impaired liver function (when appropriate dosage reduction has not been adopted) and simultaneous treatment with other myelosuppressive agents.

Immune System Disorders:
Anaphylaxis.

Metabolism and Nutrition Disorders:
Tumour lysis syndrome, anorexia, dehydration and hyperuricaemia.

Nervous System Disorders:
Somnolence, dizziness.

Eye Disorders:
Conjunctivitis / keratitis and lacrimation.

Cardiac Disorders:
Cardiotoxicity may be manifested in tachycardia including supraventricular tachycardia and ECG changes. Routine ECG monitoring is recommended and caution should be exercised in patients with impaired cardiac function. Severe cardiac failure may occur suddenly without premonitory ECG changes. Tachyarrhythmias, atrio-ventricular and bundle branch block, asymptomatic reduction in left ventricular ejection fraction and congestive heart failure.

Vascular Disorders:
Phlebitis, thrombophlebitis, thromboembolism, phlebosclerosis. hot flushes and shock.

Respiratory, thoracic and mediastinal disorders:
Dyspnoea, bronchospasm, radiation pneumonitis.

Gastrointestinal Disorders:
Nausea, vomiting and mucositis/stomatitis, hyperpigmentation of oral mucosa, oesophagitis, abdominal pain, gastric erosions, gastrointestinal tract bleeding, diarrhoea and colitis.

Hepatobiliary Disorders:
Changes in transaminase levels, hepatotoxicity.

Skin and Subcutaneous Tissue Disorders:
Alopecia occurs frequently, including the interruption of beard growth, but all hair growth normally resumes after treatment is stopped. Skin rashes/itch, local toxicity, skin changes, skin and nail hyperpigmentation, onycholysis, photosensitivity, hypersensitivity to irradiated skin ('radiation recall reaction'), urticaria, acral erythema, plantar-palmar dysaesthesia, and erythematous streaking along the vein proximal to the site of injection. Extravasation may also lead to skin necrosis, cellulitis, and vesication.

Renal and Urological Disorders:
Doxorubicin may impart a red colour to urine particularly to the first specimen passed after the injection and patients should be advised that this is no cause for alarm. Doxorubicin may also cause renal damage and haemorrhagic cystitis.

Reproductive System and Breast Disorders:
Amenorrhoea, oligospermia and azoospermia.

General Disorders and Administration Site Conditions:
The risk of thrombophlebitis at the injection site may be minimised by following the procedure for administration recommended above. A stinging or burning sensation at the site of administration signifies a small degree of extravasation and the infusion should be stopped and re-started in another vein. Fever, malaise, asthenia and chills.

Investigations:
ECG abnormalities.

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 HPRA Pharmacovigilance (Earlsfort Terrace IRL - Dublin 2). Tel: +353 1 6764971. Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Clinical Features: The symptoms of overdosage are likely to be an extension of doxorubicin's pharmacological action. Single doses of 250 mg and 500 mg of doxorubicin have proved fatal. Such doses may cause acute myocardial degeneration within 24 hours, and severe myelosuppression, the greatest effects of which are seen between 10 and 15 days after administration.

Delayed cardiac failure may occur up to six months after the overdose. Patients should be monitored carefully and if symptoms appear, conventional treatment started.

Management: Symptomatic supportive measures should be instituted. Particular attention should be given to prevention and treatment of possible severe haemorrhage or infections secondary to severe, persistent bone marrow depression. Blood transfusion and reverse barrier nursing may be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic antibiotics and related substances/anthracyclines and related substances

ATC code: L01D B01

Doxorubicin hydrochloride is a cytotoxic anthracycline antibiotic.

Although not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations.

The specificity of doxorubicin toxicity appears to be related primarily to proliferative activity of normal tissue. Thus, bone marrow, gastro-intestinal tract and gonads are the main normal tissues damaged.

Doxorubicin is not suitable for oral administration as less than 5% of the drug is absorbed.

5.2 Pharmacokinetic properties

Pharmacokinetic studies show the intravenous administration of normal or radiolabelled doxorubicin for injection is followed by rapid plasma clearance and significant tissue binding. No information on plasma-protein binding of doxorubicin is available.

The metabolism and disposition of doxorubicin is still to be defined. The drug is metabolised predominantly by the liver to doxorubicinol and several aglycone metabolites. It should be noted that several of the metabolites are cytotoxic. However, it is not certain whether any are more cytotoxic than the parent compound. High levels of metabolites appear rapidly in plasma and undergo a distribution phase with a measurable short initial half-life. Metabolism may be impaired in patients with abnormal liver function.

The disappearance of doxorubicin and its metabolites from the plasma follows a triphasic pharmacokinetic pattern with a mean half-life of the first phase of 12 minutes, of a second phase of 3.3 hours and a prolonged third phase of 29.6 hours.

Urinary excretion of doxorubicin hydrochloride and its metabolites is prolonged and accounts for only 5% of the drug excreted during the first 5 days.

Approximately 50% of an administered dose is excreted in bile.

Impairment of liver function results in slower excretion, and consequently, increased retention and accumulation in plasma and tissues. Doxorubicin does not cross the blood brain barrier. However it is known to cross the placenta barrier.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

6.2 Incompatibilities

Doxorubicin should not be mixed with heparin since it has been reported that these drugs are incompatible to the extent that a precipitate may form. It should not be mixed with 5-fluorouracil as degradation may occur. Until specific compatibility data are available, it is not recommended that doxorubicin be mixed with other drugs.

6.3 Shelf life

Prior to first use: 36 months
Unreconstituted: 3 years
In use: 24 hours

6.4 Special precautions for storage

Prior to first use: Do not store above 25^{o}C. Keep vial in the outer carton in order to protect from light.

In use: Chemical and physical in-use stability following reconstitution in either sodium chloride 0.9% or Water for Injections in glass or polypropylene containers has been demonstrated for up to 21 days at 2-8^{o}C. From a microbiological point of view, however, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours when stored at 2-8^{o}C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Once reconstituted, do not use Doxorubicin Hydrochloride Powder for Solution for Injection, if it shows evidence of precipitation or any other particulate matter.

6.5 Nature and contents of container

30 ml clear, Type I glass vial and Onco-Tain® vials, with Type I rubber closures in packs of 1 vial.

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.

Doxorubicin is a potent cytotoxic agent which should only be prescribed, prepared and administered by professionals who have been trained in the safe use of the preparation. The following guidelines should be followed when handling, preparing and disposing of doxorubicin.

Preparation

1. Reconstitution of powder, transfer to syringes or infusion bags should be carried out in designated areas, preferably a laminar flow station. The work surface should be protected by disposable plastic-backed absorbent paper.

2. Personnel must be adequately protected with suitable clothing, gloves, mask and eye shield.

3. Pregnant women should be excluded from handling cytotoxic agents.

Contamination

1. In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat transient stinging of skin. Medical advice should be sought if the eyes are affected.

2. In the event of spillage treat with 1% Sodium Hypochlorite solution using a cloth/sponge kept in the designate area. Rinse twice with water. Put all cloths into a plastic bag and seal for incineration.

Disposal

All items used during preparation or administration including syringes, containers absorbent materials, residual solutions should all be placed in a thick plastic bag and incinerated at 700^{o}C.

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

Preparation of the Injection

The contents of the vial should be reconstituted with Water for Injections, Sodium Chloride 0.9%, or 5% Glucose Intravenous Infusion to a solution concentration of 2 mg per ml.

Prolonged contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0437/026/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 June 1991
Date of last renewal: 25 June 2006

10 DATE OF REVISION OF THE TEXT

February 2016