IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0361/024/001
Case No: 2045379

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

Doxorubicin Martindale Pharma 2 mg/ml Concentrate for solution for 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 **04/09/2009** until **03/09/2014**.

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

Doxorubicin Martindale Pharma 2 mg/ml Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre of concentrate for solution for infusion contains 2 mg Doxorubicin hydrochloride.

Each 5ml vial contains a total content of Doxorubicin hydrochloride of 10 mg.
Each 10ml vial contains a total content of Doxorubicin hydrochloride of 20 mg.
Each 25ml vial contains a total content of Doxorubicin hydrochloride of 50 mg.
Each 75ml vial contains a total content of Doxorubicin hydrochloride of 150 mg.
Each 100ml vial contains a total content of Doxorubicin 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

Concentrate for solution for infusion

The product is a clear, red solution which is practically free of particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Doxorubicin is indicated in neoplastic conditions including acute leukaemia, lymphomas, soft-tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours.

Examples include:
- Small-cell lung cancer (SCLC)
- Breast cancer
- Advanced ovarian carcinoma
- Intravesically for bladder cancer
- Neoadjuvant and adjuvant therapy of osteosarcoma
- Advanced soft-tissue sarcoma in adults
- Ewing’s sarcoma
- Hodgkin’s disease
- Non-Hodgkin’s lymphoma
- Acute lymphatic leukaemia
-Acute myeloblastic leukaemia
- Advanced multiple myeloma
- Advanced or recurrent endometrial carcinoma
- Wilms’ tumour
- Advanced papillary/follicular thyroid cancer
- Anaplastic thyroid cancer
- Advanced neuroblastoma
- Advanced gastric carcinoma

Doxorubicin is frequently used in combination chemotherapy regimens with other cytostatic agents.

4.2 Posology and method of administration

Treatment with Doxorubicin should be started by or after consultation with a doctor with extensive experience from cytostatic treatment.

Due to the risk of a lethal cardiomyopathy, the risks and benefits to the individual patient should be weighted before each application.

The diluted solution is injected via the tubing of a freely-running intravenous infusion over 2-15 minutes. This technique minimizes the risk of thrombophlebitis or perivenous extravasation which can lead to severe cellulitis and vesication. (For recommended diluents see section 6.6)

Intravenous administration:
The dosage of doxorubicin depends on dosage regimen, general status and previous treatment of the patient.

Several dosage regimens exist:
The recommended dose is 60-75 mg/m² body surface i.v. as a single dose or in divided doses on 2-3 consecutive days administered with 21 day's intervals. The lower dose should be given to patients with bone marrow depression.

When Doxorubicin is administered in combination with other cytostatics, the dosage should be reduced to 30-60 mg/m² in cycles of every 3 weeks**.**

In patients, who cannot receive the full dose (eg. in case of immunosuppression, old age), an alternative dosage is 15-20 mg/m² body surface per week**.**

In order to avoid cardiomyopathy, it is recommended that the cumulative total lifetime dose of doxorubicin (including related drugs such as daunorubicin) should not exceed 450-550mg/m^2 body surface area. If patients with concomitant heart disease receive mediastinal and/or heart irradiation, prior treatment with alkylating agents or concomitant treatment with potentially cardiotoxic agents, and high-risk patients (with arterial hypertension since > 5 years, with prior coronary, valvular or myocardial heart damage, age over 70 years) a maximum total dose of 400 mg/m^2 body surface area should not be exceeded and the cardiac function of these patients should be monitored (see section 4.4)

Hepatic impairment
In cases of decreased liver function, the dosage should be reduced according to the following table:

Serum bilirubin	Recommended dose
20-50 micro mole/L	½ normal dose
> 50 micro mole/L	¼ normal dose

Doxorubicin is contraindicated in patients with severe liver function disorder (see section 4.3).

Renal impairment
In cases of renal insufficiency with a GFR less than 10 ml/min, 75% of the calculated dose should be administered.

Children
Dosage in children
Dosage for children should be reduced, since they have an increased risk for cardiac toxicity especially late toxicity. Myelotoxicity should be anticipated, with nadirs at 10 to 14 days after start of treatment. Maximal cumulative dose in children is 400 mg/m².

Obese patients
A reduced starting dose or prolonged dose interval might need to be considered in obese patients (see 4.4 **'**Special warnings and precautions for use')

Intravesical administration:
Doxorubicin can be given by intravesical instillation for treatment of superficial cancer of the bladder and to prevent relapse after transurethral resection (T.U.R). The recommended dose for intravesical treatment of superficial cancer of the bladder is 30-50 mg in 25-50 ml of physiological saline per instillation. The optimal concentration is about 1 mg/ml. The solution should remain in the bladder for 1-2 hours. During this period the patient should be turned 90° every 15 minutes. To avoid undesired dilution with urine the patient should be informed not to drink anything for a period of 12 hours before the instillation (this should reduce the production of urine to about 50 ml/h). The instillation may be repeated with an interval of 1 week to 1 month, dependent on whether the treatment is therapeutic or prophylactic.

4.3 Contraindications

Hypersensitivity to doxorubicin or other anthracyclines, to methylparahydroxybenzoate or anthracendiones

Contraindications for intravenous administration:

- Persistent myelosuppression or severe stomatitis which appeared during previous cytotoxic treatment and/or radiation
- general infection
- severe impaired liver function
- severe arrhythmia, heart failure, previous cardiac infarct, acute inflammatory heart disease
- previous treatment with anthracyclines with maximum cumulative doses
- increased haemorrhagic tendency

Contraindications of intravesical administration:

- invasive tumors that have penetrated the bladder (beyond T1)
- urinary tract infections
- inflammation of the bladder
- problems with catheterization e.g. urethral stenosis
- haematuria

Doxorubicin may not be given during pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

Patients should recover from the acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with doxorubicin.

<u>Before or during treatment with Doxorubicin the following monitoring examinations are recommended (how often these examinations are done will depend on the general condition, the dose and the concomitant medication):</u>

- radiographs of the lungs and chest and ECG
- regular monitoring of heart function (LVEF by e.g. ECG, UCG and MUGA scan)
- daily inspection of the oral cavity and pharynx for mucosal changes
- Blood tests: haematocrit, platelets, differential white cell count, SGPT, SGOT, LDH, bilirubin, uric acid.

<u>Treatment control</u>
Prior to start of the treatment it is recommended to measure the liver function by using conventional tests such as AST, ALT, ALP and bilirubin as well as the renal function.

Control of the left ventricular function
Analysis of LVEF using ultrasound or heart scintigraphy should be performed in order to optimise the heart condition of the patient. This control should be made prior to the start of the treatment and after each accumulated dose of approximately 100 mg/m²

Cardiac Function
Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e. acute) or late (i.e. delayed) events.

Early (i.e. Acute) Events: 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. As a rule, in patients with a normal LVEF baseline value (=50%), a 10% decrease of absolute value or dropping below the 50% threshold indicates cardiac dysfunction and in such situation treatment with doxorubicin hydrochloride should be carefully considered.

Late (i.e. Delayed) Events: 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. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnoea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion and gallop rhythm. 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 drug.

Cardiac function should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy to minimize 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. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.

The probability of developing CHF, estimated around 1% to 2% at a cumulative dose of 300 mg/m^2 slowly increases up to the total cumulative dose of 450-550 mg/m^2. Thereafter, the risk of developing CHF increases steeply and it is recommended not to exceed a maximum cumulative dose of 550 mg/m^2. 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-fluoruracil), cardiotoxicity with doxorubicin may occur at lower cumulative doses and cardiac function should be carefully monitored.

It is probable that the toxicity of doxorubicin and other anthracyclines or anthracenediones is additive.

Liver function
The major route of elimination of doxorubicin is the hepatobiliary system. Serum total bilirubin should be evaluated before and during treatment with doxorubicin. Patients with elevated bilirubin may experience slower clearance of the drug with an increase in overall toxicity. Lower doses are recommended in these patients (see section 4.2 Posology and Method of Administration). Patients with severe hepatic impairment should not receive doxorubicin (see section 4.3 Contraindications).

Haematologic Toxicity
Doxorubicin may produce myelosuppression (See Section 4.8) Haematologic profiles should be assessed before and during each cycle of therapy with doxorubicin, including differential white blood cell (WBC) counts. A dose-dependent, reversible leucopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leucopenia and neutropenia generally reach the nadir between days 10 and 14 after drug administration; the WBC/neutrophil counts return to normal values in most cases by day 21. Dose reduction or increase of the dose interval should be considered if the blood values are not normalised. Thrombocytopenia and anaemia may also occur. Clinical consequences of severe myelosuppression include fever, infections, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

Secondary Leukaemia
Secondary leukaemia, with or without a preleukaemic phase, has been reported in patients treated with anthracyclines. Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, when patients have been heavily pretreated with cytotoxic drugs or when doses of the anthracyclines have been escalated. These leukaemias can have a 1 to 3 year latency period.

Carcinogenesis, Mutagenesis and Impairment of Fertility
Doxorubicin was genotoxic and mutagenic *in vitro* and *in vivo* tests.

In women, doxorubicin may cause infertility during the time of drug administration. Doxorubicin may cause amenorrhoea (see section 4.8). Ovulation and menstruation appear to return after termination of therapy, although premature menopause can occur.

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 methods.

Men and woman who are sexually active and undergoing doxorubicin treatment should use effective contraceptive methods.

Intravesical 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).
Intravesical administration is contraindicated for tumours that have penetrated the bladder (beyond T1).
The intravesical route of administration should not be attempted in patients with, invasive tumours that have penetrated the bladder wall, urinary tract infections, inflammatory conditions of the bladder.

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 Martindale Pharma 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/m² must not be exceeded especially in this case.

Anticancer therapies:
Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhanced hepatotoxicity of 6-mercaptopurine have been reported.
As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena including pulmonary embolism (in some cases fatal) have been coincidentally reported with the use of doxorubicin (see section 4.8 ‘Undesirable effects’).

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

Other:
The systemic clearance of doxorubicin is reduced in obese patients (i.e. >130% ideal body weight) (see section 4.2 Posology and Method of Administration).

Doxorubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies drug-induced rapid lysis of neoplastic cells (tumour-lysis syndrome) (see section 4.8 'Undesirable effects'). Blood uric acid levels, potassium, calcium phosphate and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricaemia may minimize potential complications of tumour lysis syndrome.

The patient should be informed that the urine might be reddish, particularly in the first specimen after administration, but that this is no cause for alarm.

A stinging or burning sensation at the site of administration may signify a small degree of extravasation. If extravasation is suspected or occurs, the injection should be discontinued and restarted in a different blood vessel. Cooling the area for 24 hours can reduce the discomfort. The patient should be carefully monitored for several weeks. Surgical measures might be necessary (see section 4.8 'Undesirable effects')

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 other potentially cardiotoxic drugs (e.g. 5-fluorouracile, cyclophosphamide or paclitaxel) or with products affecting cardiac function (like calcium antagonists). When doxorubicin is used together with the above mentioned agents, cardiac function must be followed carefully.

The use of trastuzumab in combination with anthracyclines (such as doxorubicin) is associated with a high cardiotoxic risk. Trastuzumab and anthracyclines should not be used in combination for the time being, except in well controlled clinical studies where the cardiac function is monitored. When anthracyclines are used after the end of a therapy with trastuzumab, an elevated risk of cardiotoxicity may result. If possible, there should be a sufficiently long interval (up to 22 weeks) between the end of a therapy with trastuzumab and the beginning of the anthracycline therapy. Careful monitoring of the cardiac function is imperative.

Doxorubicin hepatotoxicity may be enhanced by other hepatotoxic treatment modalities (e.g. 6-mercaptopurine).

Doxorubicin undergoes metabolism via Cytochrome P450 (CYP450) and is a substrate for the 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 by 55% and 350%, respectively. The combination might require dose adjustment. Cimetidine has also been shown to reduce the plasma clearance and increase the AUC of doxorubicin.

Paclitaxel administered shortly before doxorubicin may decrease clearance and increase plasma concentrations of doxorubicin. Some data indicate that this interaction is less pronounced when doxorubicin is administered before paclitaxel.

Barbiturates may lead to an accelerated plasma clearance of doxorubicin, while 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 a doxorubicin therapy may be increased in a combination with other cytostatics (e.g.cytarabine, cisplatin, cyclophosphamide)._Necroses of the large intestine with massive haemorrhage and severe infections in connection with combination therapies with cytarabine.
Clozapine may increase the risk and severity of the hematologic toxicity of Doxorubicin

Marked nephrotoxicity of Amphotericin B can occur during doxorubicin therapy.

As doxorubicin is rapidly metabolised 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. This applies also to concomitant therapies with cardiotoxic or hepatotoxic drugs.

Doxorubicin may cause exacerbations of hemorrhagic cystitis caused by previous cyclophosphamide therapy.

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.

During treatment with Doxorubicin patients should not be actively vaccinated and also avoid contact with recently polio vaccinated persons.

4.6 Pregnancy and lactation

Pregnancy:
Doxorubicin should not be given during pregnancy. In general cytostatics should only be administered during pregnancy on strict indication, and the benefit to the mother weighed against possible hazards to the foetus. In animal studies, doxorubicin has shown embryo-, foeto- and teratogenic effects (see 5.3 Preclinical safety data).
Men and women should use effective contraception during and up to 6 months after treatment.

Lactation:
Doxorubicin has been reported to be excreted in human breast milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with doxorubicin.

4.7 Effects on ability to drive and use machines

Due to the frequent occurrence of nausea and vomiting, driving cars and operation of machinery should be discouraged.

4.8 Undesirable effects

Treatment with doxorubicin often causes undesirable effects, and some of these effects are serious enough to entail careful monitoring of the patient. The frequency and kind of undesirable effects are influenced by the speed of administration and the dosage. Bone-marrow suppression is an acute dose limiting adverse effect, but is mostly transient. Clinical consequences of doxorubicin bone marrow/haematological toxicity may be fever, infections, sepsis/septicaemia, septic shock, haemorrhages, tissue hypoxia or death. Nausea and vomiting as well as alopecia are seen in almost all patients.

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).

	Common	Uncommon	Rare	Not known
Infections and infestations	Sepsis, septiciaemia			
Neoplasms benign and malignant			Secondary leukaemia when in combination with anti-neoplastic drugs which damage the DNA. (see section 4.4), tumour lysis syndrome	
Blood and lymphatic system disorders:	bone-marrow suppression, leucopenia and neutropenia			Thrombocytopenia, anaemia
Immune System disorders			Anaphylactic reactions	
Endocrine disorders				Hot flushes
Eye disorders			conjunctivitis	
Cardiac disorders	cardiomyopathy (2%; e.g. decrease of LVEF, dyspnoea); ECG changes (e.g. sinus tachycardia, tachyarythmia, ventricular tachycardia, bradycardia, bundle branch block)			arrhythmia, heart failure
Vascular disorders		phlebitis		Thrombophlebitis; thromboembolism
Gastrointestinal disorders:	nausea; vomiting; mucositis; anorexia; diarrhoea	Gastrointestinal haemorrhage, abdominal pain ; ulceration of the mucous membranes in the mouth, pharynx , oesophagus and gastrointestinal tract may appear; in combination with cytarabine, ulceration and necrosis of the colon, in particular the caecum, have been reported (see section 4.5)		
Respiratory, thoracic and mediastinal disorders				Bronchospasm, radiat ion pneumonitis

Skin and subcutaneous tissue disorders:	alopecia	Itching, local hypersensitivity reaction of the field of radiation (recall phenomenon)	urticaria, exanthema, local erythematous reactions along the vein which was used for the injection, hyperpigmentation of skin and nails, onycholysis	tissue hypoxia
Renal and urinary disorders:	local reactions (chemical cystitis) might occur at intravesical treatment (i.e. dysuria, urinary frequency, nocturia, stranguria, haematuria, necrosis of the bladder wall)			acute renal failure, hyperuricaemia (see section 4.4)
Reproductive system and breast disorders				Amenorrhoea, oligospermia, azoospermia (see section 4.4)
General disorders and administration site conditions:		dehydration	anaphylactic reactions, shivering, fever, dizziness	A stinging or burning sensation at the administration site (see section 4.4) Malaise/weakness
Hepatobiliar disorders				Hepatotoxicity, transient increase of liver enzymes
Surgical and medical procedure				Extravasation can lead to severe cellulitis, vesication and local tissue necrosis which may require surgical measures (including skin grafts) (see section 4.4)

4.9 Overdose

Acute overdosage of doxorubicin may lead to myelosuppression (particularly leucopenia and thrombocytopenia), generally 10 – 14 days following overdose, gastrointestinal toxic effects (particularly mucositis) and acute cardiac alterations, which may occur within 24 hours. Treatment includes intravenous antibiotics, transfusion of granulocytes and thrombocytes and treatment of the gastrointestinal symptoms and heart effects. Moving the patient to a sterile room and the use of a haemopoietic growth factor should be considered.
Single doses of 250 mg and 500 mg of doxorubicin have proved fatal.

Chronic overdosage, with a cumulative dose exceeding 550 mg/m^2 increases the risk for cardiomyopathy and may lead to heart failure, which should be treated along conventional lines. Delayed cardiac failure may occur up to six months after the overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances)
ATC code: L01DB01

Doxorubicin is an anthracycline antibiotic. The mechanism of action is not completely elucidated. It is postulated that Doxorubicin Martindale Pharma exerts its antineoplastic effect via cytotoxic mechanisms of action, especially intercalation into DNA, inhibition of the enzyme topoisomerase II, and formation of reactive oxygen species (ROS). All of these have a deleterious effect on DNA synthesis: Intercalation of the doxorubicin molecule leads to an inhibition of RNA and DNA polymerases by way of disturbances in base recognition and sequence specificity. The inhibition of topoisomerase II produces single and double strand breaks of the DNA helix. Scission of DNA also originates from the chemical reaction with highly reactive oxygen species like the hydroxyl radical $OH^{\bullet}$. Mutagenesis and chromosomal aberrations are the consequences.

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.

An important cause of treatment failure with doxorubicin and other anthracyclines is the development of resistance. In an attempt to overcome cellular resistance to doxorubicin, the use of calcium antagonists such as verapamil has been considered since the primary target is the cell membrane. Verapamil inhibits the slow channel of calcium transport and can enhance cellular uptake of doxorubicin. A combination of doxorubicin and verapamil is associated with severe cardiotoxic effects.

5.2 Pharmacokinetic properties

Distribution
Following intravenous injection, doxorubicin is rapidly cleared from the blood, and widely distributed into tissues including lungs, liver, heart, spleen, lymph nodes, bone marrow and kidneys. The volume of distribution is about 25 litres. The degree of protein binding is 60-70%.

Doxorubicin does not cross the blood-brain barrier, although higher levels in liquor may be reached in the presence of brain metastases or leukemic cerebral dissemination. Doxorubicin is rapidly distributed into the ascites, where it reaches higher concentrations than in plasma. Doxorubicin is secreted into breast milk.

Elimination
The elimination of doxorubicin from the blood is triphasic with mean half-lives of 12 minutes (distribution), 3.3 hours and about 30 hours. Doxorubicin undergoes rapid metabolism in the liver. The main metabolite is the pharmacologically active doxorubicinol. Other metabolites are deoxyrubicin aglycone, glucuronide and sulphate conjugate. About 40 to 50% of a dose is excreted in bile within 7 days, of which about half is excreted as unchanged drug and the rest as metabolites. Only 5-15 % of the administered dose is eliminated in urine.

Special populations
As the elimination of doxorubicin is mainly hepatic, impairment of liver function results in slower excretion, and consequently, increased retention and accumulation in plasma and tissues. Dose reduction is generally advised.

Although renal excretion is a minor elimination pathway for doxorubicin, severe renal impairment might affect total elimination and require dose reduction.

In a study in obese patients (>130% of ideal bodyweight) the doxorubicin clearance was reduced and the half life increased compared with a normal-weight control group. Dose adjustments might be necessary in the obese.

5.3 Preclinical safety data

Animal studies from literature show that doxorubicin affects the fertility, is embryo- and foetotoxic and teratogenic. Other data shows that doxorubicin is mutagenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Contact with any solution of an alkaline pH should be avoided as it will result in hydrolysis of the drug. Doxorubicin should not be mixed with heparin and 5-fluorouracil since a precipitate may form, and it is not recommended that doxorubicin be mixed with other drugs until specific compatibility data are available.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.3.

6.3 Shelf Life

Unopened vials: 2 years

Opened vials: The product should be used immediately after opening the vial.
Prepared infusion solutions:
Following dilution the prepared solution should be refrigerated in order to protect from light.
Chemical and physical in-use stability has been demonstrated in sodium chloride 0.9 % or glucose 5 % for up to 48 hours at 2 – 8°C and for up to 24 hours at 25°C when prepared in PVC infusion bags and polypropylene syringes 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° C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Keep the container in the outer carton in order to protect from light.

For storage conditions of the reconstituted product see section 6.3.

6.5 Nature and contents of container

Colourless glass vials (type I glass) with chlorobutyl rubber stoppers with ETFE (ethylene tetrafluoroethylene – fluorocarbon-based polymer) layer.

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 75 ml vial (150 mg/75 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

For single use only. Dilute before use

Observe guidelines for handling cytotoxic drugs.

The following protective recommendations are given due to the toxic nature of this substance:

- Personnel should be trained in good technique for handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling doxorubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
- All items used for administration or cleaning, including gloves, should be placed in high risk waste disposal bags for high temperature (700°C) incineration.

Accidental contact with the skin should be treated immediately by copious lavage with water or soap and water. In an accidental contact, the eyes should be rinsed copiously with water or sodium bicarbonate solution. Medical attention should be sought.

Spillage or leakage should be treated with dilute sodium hypochlorite (1 % available chlorine) solution, preferably soaking overnight and then rinse with water.

All cleaning materials should be disposed of as indicated previously.

Doxorubicin Martindale Pharma should be further diluted in Sodium Chloride 0.9% or Glucose 5% and administered as an intravenous infusion. The infusion solution should be prepared immediately before use.

7 MARKETING AUTHORISATION HOLDER

Martindale Pharmaceuticals Limited
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Harold Hill
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8 MARKETING AUTHORISATION NUMBER

PA 361/24/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th September 2009

10 DATE OF REVISION OF THE TEXT