

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ADRIAMYCIN 2 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of ADRIAMYCIN contains 10 mg, 20 mg, 50 mg and 200 mg of doxorubicin hydrochloride as a solution (2 mg/mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Doxorubicin has produced significant therapeutic responses in a number of solid tumours and haematologic malignancies, and is commonly used in the treatment of the following tumours:

- carcinoma of the breast
- carcinoma of the lung
- carcinoma of the ovary
- transitional bladder cell cancer
- neuroblastoma
- Wilms' tumour
- soft tissue sarcomas
- osteosarcoma
- acute lymphocytic - lymphoblastic leukaemia
- acute myelogenous leukaemia
- non-Hodgkin's lymphoma
- Hodgkin's disease

Doxorubicin has also shown antitumour activity in the following adult and paediatric malignancies:

- carcinoma of the thyroid
- carcinoma of the endometrium

- carcinoma of the head and neck
- carcinoma of the stomach
- primary hepatocellular carcinoma
- non-seminomatous carcinoma of the testis
- carcinoma of the prostate
- Ewing's sarcoma
- rhabdomyosarcoma
- multiple myeloma
- chronic leukaemias

4.2 Dose and method of administration

Dose

Doxorubicin is a cytotoxic drug that is usually administered to cancer patients by the intravenous and, whenever appropriate, intravesical and intra-arterial routes.

Intravenous (IV) Administration:

Dosage is usually calculated on the basis of body surface area (mg/m^2). The doxorubicin dose-schedule to be delivered may differ depending on the therapeutic indication (e.g., solid tumours or acute leukaemias) as well as on its use within a specific regimen (e.g., as a single agent or in combination with other cytotoxics or as a part of multidisciplinary approaches which include combination with surgery and/or radiotherapy and/or hormonotherapy).

Intravenous administration of doxorubicin should be performed with caution. It is recommended to administer doxorubicin into the tubing of a freely flowing IV infusion (isotonic sodium chloride or 5% glucose solution) over a period of 3 to 5 minutes. This technique is intended to minimize the risk of thrombosis or perivenous extravasation which could lead to severe cellulitis, vesication and tissue necrosis. A direct push injection is not recommended due to the risk of extravasation, which may occur even in the presence of adequate blood return upon needle aspiration.

Treatment of solid tumours: When doxorubicin is administered as a single agent, the recommended dose per cycle is $60\text{-}75 \text{ mg}/\text{m}^2$ every three weeks. The drug is generally given as a single dose per cycle; however, it is possible to give the drug dosage per cycle in divided administrations (e.g., day 1 through 3, or days 1 and 8).

Administration of doxorubicin in a weekly regimen has been shown to be as effective as the tri-weekly schedule. The recommended weekly dosage is $10\text{-}20 \text{ mg}/\text{m}^2$; this schedule of administration might be accompanied by reduced toxicity, particularly on the heart.

If doxorubicin is used in combination with other antitumour agents with potentially overlapping toxicities, the recommended dose per cycle is in the $30\text{-}60 \text{ mg}/\text{m}^2$ range.

Treatment of acute leukaemias: In the management of acute leukaemias, bone marrow aplasia is a therapeutic achievement and intensive combination chemotherapy schedules are employed. In this situation the recommended dose of doxorubicin is 2.4 mg/kg of body weight (approximately corresponding to 75-90 mg/m²), to be administered divided over three consecutive days (one cycle). The time and dose of the second cycle should be dictated by both the bone marrow and peripheral blood cells status. The interval between cycles should be however at least 10 days.

Dosage Adjustments

Hepatic impairment: In the presence of impaired hepatic function it is suggested to reduce doxorubicin dosage (see section 4.4).

Dose reductions are recommended in patients with the following serum chemistry values:

- Bilirubin 1.2 to 3 mg/dL: ½ of recommended starting dose
- Bilirubin > 3 mg/dL: ¼ of recommended starting dose

Doxorubicin should not be administered to patients with severe hepatic impairment (see section 4.3).

Other special populations: Lower starting doses or longer intervals between cycles may need to be considered for heavily pretreated patients, children, elderly patients, obese patients, or patients with neoplastic bone marrow infiltration (see section 4.4).

Intravesical Administration:

Doxorubicin administered intravesically can be used for the treatment of superficial bladder tumours or as prophylaxis to reduce recurrence after trans-urethral resection. The recommended doxorubicin dose for topical intravesical treatment of superficial bladder cancer is 30 to 50 mg in 25 – 50 mL of saline solution per instillation, with the optimal concentration being in the 1.0 mg/mL range. In the case of local toxicity (chemical cystitis), the dose should be instilled in 50-100 mL of saline solution. Once the instillation has been completed, the patients should be rotated a quarter turn every fifteen minutes. Generally, the instillate should be retained in the bladder for 1-2 hours. To avoid undue dilution with urine, the patients should be instructed not to drink any fluid in the twelve hours prior to instillation (this should limit urine production to approximately 50 mL/hour). The patient should be instructed to void at the end of the installation. Instillations can be repeated at intervals which can vary from one week to one month, depending on whether the treatment is therapeutic or prophylactic. The systemic absorption of doxorubicin following intravesical instillation is very low.

Intra-arterial Administration:

Doxorubicin has been also used by the intra-arterial route in an attempt to produce intense local activity with reduced general toxicity in patients with hepatocellular carcinoma. Since this technique is potentially hazardous and can lead to widespread necrosis of the perfused tissue, intra-arterial administration should only be attempted by those physicians fully trained with this technique. Patients may receive an infusion into the main hepatic artery in doses of 30 to 150 mg/m² at intervals of 3 weeks to 3 months, with higher doses reserved for

administration with concurrent extracorporeal drug elimination. Lower doses are suitable for administration of doxorubicin with iodised oil.

Method of Administration

ADRIAMYCIN is supplied as a solution for injection.

Storage of the ADRIAMYCIN solution at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after two to a maximum of four hours equilibration at controlled room temperature (15 - 25°C).

Intravenous administration: Doxorubicin is usually administered intravenously. The solution should be injected over 3 to 5 minutes through the tubing of a freely-running infusion of physiological solution, after confirmation that the needle is correctly inserted into the vein. This technique reduces the risk of thrombosis and perivenous extravasation of the drug that can lead to severe cellulitis and necrosis, and ensures the washing of the vein after administration. Injection in small veins and repeated injection in the same vein can lead to venous sclerosis.

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

- personnel should be trained in good technique and 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;
- A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed, absorbent paper.
- all items used for, administration or cleaning, including gloves, should be placed in high-risk waste-disposal bags for high-temperature incineration.
- 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 indicated previously.
- 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.
- In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

4.3 Contraindications

Hypersensitivity to doxorubicin or any other component of the product, other anthracyclines or anthracenediones. ADRIAMYCIN therapy is also contraindicated in pregnancy and lactation.

Intravenous (IV) use:

Situations in which patients should not be treated with IV intravenous doxorubicin are:

- persisting myelosuppression or severe stomatitis from previous cytotoxic treatments;
- presence of generalised infections;
- marked liver function impairment;
- severe arrhythmias, myocardial insufficiency, previous myocardial infarction;
- previous treatment with anthracyclines up to their maximum cumulative dose;

Intravesical use:

Contraindications for intravesical use are:

- invasive tumours that have penetrated the bladder wall;
- urinary infections;
- inflammation of the bladder;
- catheterisation problems (e.g., due to massive intravesical tumours).
- Haematuria

4.4 Special warnings and precautions for use

General

Doxorubicin should be administered only under the supervision of physicians experienced in the use of cytotoxic therapy.

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

Cardiac Function

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

Early (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 effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not a consideration for discontinuation of doxorubicin treatment.

Late (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 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. 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/m², slowly increases up to the total cumulative dose of 450-550 mg/m². Thereafter, the risk of developing CHF increases steeply, and it is recommended not to exceed a maximum cumulative dose of 550 mg/m².

Cardiac function must be carefully monitored in patients receiving high cumulative doses and in those with risk factors. However, cardiotoxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present. Risk factors for cardiac toxicity include a previous history of heart disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous treatments with anthracyclines or anthracenediones, concomitant use of other cardioactive compounds (e.g., calcium channel blocking drugs) or concomitant use of other potentially cardiotoxic drugs (e.g., cyclophosphamide, 5-fluorouracil or trastuzumab). Anthracyclines including doxorubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored (see section 4.5). Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity.

The half-life of trastuzumab is variable. Trastuzumab may persist in the circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Children and adolescents are at an increased risk for developing delayed cardiotoxicity following doxorubicin administration. Females may be at greater risk than males. Follow-up cardiac evaluations are recommended periodically to monitor for this effect.

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

Haematologic Toxicity

As with other cytotoxic agents, doxorubicin may produce myelosuppression. 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 leukopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin haematologic toxicity and is the most common acute dose-limiting toxicity of this drug. Leukopenia 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. 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 (including doxorubicin). Secondary leukaemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, in combination with radiotherapy, 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.

Gastrointestinal

Doxorubicin is emetigenic. Mucositis/stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations. Most patients recover from this adverse event by the third week of therapy.

Hepatic Impairment

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 drug with an increase in overall toxicity. Lower doses are recommended in these patients (see section 4.2). Patients with severe hepatic impairment should not receive doxorubicin (see section 4.3).

Obesity

The systemic clearance of doxorubicin is reduced in obese patients (i.e., >130% ideal body weight; see section 4.2, Other Special Populations).

Effects at Site of Injection

Phleboscrosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see 4.2 Dose and method of administration).

Extravasation

Extravasation of doxorubicin during IV injection may give rise to severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs of symptoms of extravasation occur during intravenous administration of doxorubicin, the drug infusion should be immediately terminated.

Tumor-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.

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents, including doxorubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving doxorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Dental Work

Patients should not undergo dental work during treatment with doxorubicin.

Other

Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhanced hepatotoxicity of 6-mercaptopurine have been reported. Radiation-induced toxicities (myocardium, mucosae, skin and liver) have also been reported to increase.

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.

Doxorubicin may impart a red colour to the urine. Patients should be advised that such an event should not be cause for alarm.

Additional Warnings and Precautions for Other Routes of Administration

Intravesical Route. Administration of doxorubicin by the intravesical route may produce symptoms of chemical cystitis (such as dysuria, polyuria, nocturia, stranguria, haematuria, bladder discomfort, necrosis of the bladder wall) and bladder constriction. Special attention is required for catheterisation problems (e.g., urethral obstruction due to massive intravesical tumours.) (see section 4.3).

Intra-arterial Route. Intra-arterial administration of doxorubicin (transcatheter arterial embolisation) may be employed for the localized or regional therapy of primary hepatocellular carcinoma or liver metastases. Intra-arterial administration may produce (in addition to systemic toxicity qualitatively similar to that observed following intravenous administration of doxorubicin) gastro-duodenal ulcers (probably due to reflux of the drugs into the gastric artery) and narrowing of bile ducts due to drug-induced sclerosing cholangitis. This route of administration can lead to widespread necrosis of the perfused tissue.

4.5 Interaction with other medicines and other forms of interaction

Doxorubicin is mainly used in combination with other cytotoxic drugs and additive toxicity may occur especially with regard to bone marrow/haematologic and gastro-intestinal effects (see section 4.4). In addition, the concomitant use of doxorubicin and other antitumour drugs which have been reported as potentially cardiotoxic (e.g., 5-fluorouracil, cyclophosphamide, cisplatin, taxanes), as well as the concomitant use of other cardioactive compounds (e.g., calcium channel blockers), requires a close monitoring of cardiac function throughout treatment.

Paclitaxel can cause increased plasma-concentration of doxorubicin and/or its metabolites when given prior to doxorubicin. Certain data indicate that this effect is minor when anthracycline is administered prior to paclitaxel.

Sorafenib: Both increases (21% - 47%) and no change in the AUC of doxorubicin were observed with concomitant treatment with sorafenib 400 mg twice daily. The clinical significance of these findings is unknown.

Doxorubicin is extensively metabolized by the liver and is a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). Changes in hepatic function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity. Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (e.g., verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (e.g., phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin.

The addition of cyclosporine to doxorubicin may result in increases in area under the concentration-time curve (AUC) for both doxorubicin and doxorubicinol, possibly due to a decrease in clearance of the parent drug and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and prolonged haematologic toxicity than that observed with doxorubicin alone. Coma and seizures have also been described with concomitant administration of cyclosporine and doxorubicin.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safe use of doxorubicin in pregnancy has not been established. Doxorubicin is embryotoxic and teratogenic in rats. The embryotoxic potential of doxorubicin was confirmed in vitro and in vivo. When given to female rats before and during mating, pregnancy, and lactation, doxorubicin was toxic to both dams and fetuses

Doxorubicin has been implicated in causing fetal harm when administered to a pregnant woman. If a woman receives doxorubicin during pregnancy or becomes pregnant while taking the drug, she should be apprised of the potential hazard to the fetus.

Breast-feeding

Doxorubicin is secreted into breast milk. Women should not breastfeed while undergoing treatment with doxorubicin.

Fertility

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

Doxorubicin was toxic to male reproductive organs in animal studies, producing testicular atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia.

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.

4.7 Effects on ability to drive and use machinery

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

4.8 Undesirable effects

Adverse reactions reported in association with doxorubicin therapy are listed below by MedDRA System Organ Class and by frequency. Frequencies are defined as: Very common ($\geq 10\%$), Common ($\geq 1\%$, $< 10\%$), Uncommon ($\geq 0.1\%$, $< 1\%$), Rare ($\geq 0.01\%$, $< 0.1\%$), Very rare ($< 0.01\%$), and Not known (cannot be estimated from available data).

Adverse Reactions Table

Infections and Infestations	
Very common	Infection
Common	Sepsis

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	
Not known	Acute lymphocytic leukaemia, Acute myeloid leukaemia
Blood and Lymphatic System Disorders	
Very common	Leukopenia, Neutropenia, Anaemia, Thrombocytopenia
Immune System Disorders	
Not known	Anaphylactic reaction
Metabolism and Nutrition Disorders	
Very common	Decreased appetite
Not known	Dehydration, Hyperuricaemia
Eye Disorders	
Common	Conjunctivitis
Not known	Keratitis, Lacrimation increased
Cardiac Disorders	
Common	Cardiac failure congestive, Sinus tachycardia
Not known	Atrioventricular block, Tachyarrhythmia, Bundle branch block
Vascular Disorders	
Uncommon	Embolism
Not known	Shock, Haemorrhage, Thrombophlebitis, Phlebitis, Hot flush
Gastrointestinal Disorders	
Very common	Mucosal inflammation/Stomatitis, Diarrhoea, Vomiting, Nausea
Common	Oesophagitis, Abdominal pain
Not known	Gastrointestinal haemorrhage, Gastritis erosive, Colitis, Mucosal discolouration
Skin and Subcutaneous Tissue Disorders	
Very common	Palmar-plantar erythrodysesthesia syndrome, Alopecia
Common	Urticaria, Rash, Skin hyperpigmentation, Nail hyperpigmentation
Not known	Photosensitivity reaction, Recall phenomenon, Pruritus, Skin disorder
Renal and Urinary Disorders	
Not known	Chromaturia ^a
Reproductive System and Breast Disorders	
Not known	Amenorrhoea, Azoospermia, Oligospermia
General Disorders and Administration Site Conditions	
Very common	Pyrexia, Asthenia, Chills

Common	Infusion site reaction
Not known	Malaise
Investigations	
Very common	Ejection fraction decreased, Electrocardiogram abnormal, Transaminases abnormal, Weight increased ^b ,
^a For one to two days after administration	
^b Reported in patients with early breast cancer receiving doxorubicin-containing adjuvant therapy (NSABP B-15 trial)	

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Acute overdosage with doxorubicin will result in severe myelosuppression (mainly leukopenia and thrombocytopenia), gastrointestinal toxic effects (mainly mucositis) and acute cardiac alterations. Treatment of acute overdosage consists of hospitalization, intravenous antibiotics, granulocyte and platelet transfusions and treatment of the gastrointestinal and cardiac toxic manifestations. The use of haematopoietic growth factors may be considered. Chronic overdosage, when total cumulative doses exceed 550 mg/m², increases the risk of cardio-myopathy and could result in CHF. For such an occurrence, treatment is that for CHF, consisting of digitalis preparations, diuretics, peripheral vasodilators and ACE inhibitors.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Although it is known that anthracyclines are able to interfere with a number of biochemical and biological functions within eukaryotic cells, the precise mechanisms of doxorubicin cytotoxic and/or antiproliferative properties have not been completely elucidated. The drug, once penetrated into a cell, mostly binds to chromatin. Experimental evidence indicates that doxorubicin forms a complex with the DNA by intercalation of its planar rings between nucleotide base pairs. The consequences of this intercalation are serious disturbances of DNA synthesis, DNA-dependent RNA synthesis and protein synthesis. However, the doxorubicin concentrations required to exert antiproliferative effects through these mechanisms appear somewhat greater than those achievable at the tumour site in the clinical setting. More recent experimental evidence seems to indicate that DNA intercalation triggers DNA cleavage by topoisomerase-II, yielding serious disturbances in the tertiary structure of

DNA. This effect is seen with drug concentrations which have been found within the clinically therapeutic range. Doxorubicin is also known to be involved in oxidation/reduction reactions: a number of NADPH-dependent cellular reductases are able to reduce doxorubicin to semiquinone free radicals, which can in turn react with molecular oxygen to generate highly reactive cytotoxic compounds such as superoxide, hydroxyl radicals and hydrogen peroxide. Free radical formation has been implicated in doxorubicin cardiotoxicity. A further site of action for doxorubicin may be at the cell membrane level: the drug can bind to cell membrane lipids and affect a variety of functions. Cytotoxicity and/or antiproliferative activity of doxorubicin may result as a consequence of any mentioned mechanisms and there may be others.

Cell kinetic studies have shown that doxorubicin is active throughout the cell cycle, including the interphase. Rapidly proliferating tissues such as tumour tissues (but also bone marrow, gastrointestinal and oral mucosa, hair follicles) are therefore the most sensitive to the antiproliferative effects of doxorubicin.

5.2 Pharmacokinetic properties

Absorption

Doxorubicin is not absorbed by the gastrointestinal tract. Since the drug is extremely irritating to tissues, it has to be administered by intravascular routes (intravenous or intra-arterial). Intravesical administration has been demonstrated as feasible; following such administration, drug passage to the systemic circulation is minimal.

Distribution

Doxorubicin is quickly and widely distributed into the extravascular compartments, as indicated by a rapid (5 to 10 min) initial plasma half-life and by a steady-state distribution volume in excess of 20 to 30 L/kg. However, doxorubicin does not cross the blood-brain barrier in detectable amounts. Binding of doxorubicin to plasma protein is about 75%, and is not dependent on plasma concentrations up to 2 μM .

Biotransformation

Doxorubicin is metabolized to a significant extent, mainly by the liver. The major metabolite of doxorubicin is 13-OH-doxorubicinol, produced by aldo-keto reductases, which possesses a certain degree of antitumour activity. Doxorubicin and 13-OH-doxorubicinol predominate also in urine and in the bile. Other metabolites present in detectable amounts in plasma are the aglycones of doxorubicin and 13-OH-doxorubicinol.

Elimination

Following IV administration, plasma levels of doxorubicin follow a multiphasic decline, with a terminal half-life reported in the 20 to 48 hour range. The terminal half-life of 13-OH-doxorubicinol is similar to that of doxorubicin. Plasma clearance is in the range of 8 to 20 ml/min/kg, and is mainly due to metabolism and biliary excretion. This slow elimination from plasma might be further prolonged in patients with impaired liver function. The clearance of doxorubicin occurs to a substantial extent by metabolic conversion to a number of less active or inactive products. Forty to fifty percent of the administered dosage is

recovered in the bile or in the faeces in seven days. Renal excretion is modest, accounting for only 5% to 10% of the administered dose in 5 days.

5.3 Preclinical safety data

The LD₅₀ of doxorubicin was 21.9 and 12.5 mg/kg for mice and rats, respectively, and about 2.0 mg/kg for dogs. The main targets after a single drug dose were the haemolymphopoietic system and, especially in dogs, the gastrointestinal tract. The toxic effects after repeated administration were investigated in rats, rabbits and dogs. The main targets of doxorubicin in the abovementioned species were the haemolymphopoietic system, the gastro-intestinal tract, the kidneys, the liver and both male and female reproductive organs. Concerning the heart, acute, subacute and cardiotoxicity studies have indicated that doxorubicin was cardiotoxic in all the laboratory animals tested.

Genotoxicity

Doxorubicin was genotoxic in a battery of *in vitro* or *in vivo* tests. An increase in the incidence of mammary tumours was reported in rats, and a trend for delay or arrest of follicular maturation was seen in female dogs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Hydrochloric acid,
Water for injections.

6.2 Incompatibilities

Doxorubicin should not be mixed with other drugs. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin.

Doxorubicin should not be mixed with heparin due to chemical incompatibility that may lead to precipitation.

Doxorubicin should not be mixed with fluorouracil (e.g., in the same IV infusion bag or at the Y-site of an IV infusion line) since it has been reported that these drugs are chemically incompatible to the extent that a precipitate might form. If concomitant therapy with doxorubicin and fluorouracil is required, it is recommended that the IV line be flushed between the administration of these drugs.

Doxorubicin should not be mixed with other cytotoxic drugs in the same vial or syringe during the administration of combination chemotherapy regimens.

6.3 Shelf life

24 months

6.4 Special precautions for storage

The solution is to be stored under refrigeration (2 to 8°C, do not freeze) and should be protected from sunlight and retained in the carton until time of use. Storage of the solution for injection at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after two to a maximum of four hours equilibration at controlled room temperature (15 to 25°C).

6.5 Nature and contents of container

ADRIAMYCIN solution for injection 10 mg in 5 mL*, 20 mg in 10 mL*, 50 mg in 25 mL and 200 mg in 100 mL are supplied in a single plastic polypropylene vial, packaged in a single vial carton.

* These presentations are not marketed.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

02 August 1990

10. DATE OF REVISION OF THE TEXT

11 February 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformat to MedSafe Data Sheet guidance
4.4	The wash-out period for the agent trastuzumab is changed to increase to 7 months. Updated to align with the company held Core Data

	Sheet (CDS).
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