PRODUCT INFORMATION

ADRIAMYCIN® Solution for Injection

WARNINGS

1. **For intravenous or intravesical use only.** Severe local tissue necrosis will occur if there is extravasation during administration. ADRIAMYCIN must not be given by the intramuscular or subcutaneous route.

2. Serious irreversible myocardial toxicity with delayed congestive failure often unresponsive to any cardiac supportive therapy may be encountered as total dosage approaches 550 mg/m².

   This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy.

3. Dosage should be reduced in patients with impaired hepatic function.

4. Severe myelosuppression may occur.

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

NAME OF MEDICINE

Non-proprietary name: doxorubicin hydrochloride

The structural formula of doxorubicin hydrochloride is shown below:

![Structural formula of doxorubicin hydrochloride](image)

CAS Registry Number: 25316-40-9

Chemical name: (8S,10S)-10-[(3-Amino-2,3,6-trIDEOXY-α-L-lyxo-hexopyranosyl)oxy]-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione hydrochloride

Molecular formula: C_{27}H_{29}NO_{11},HCl

Molecular weight: 580.0
DESCRIPTION

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius var. caesius*. Doxorubicin hydrochloride is an orange-red, crystalline, hygroscopic powder that is soluble in water and slightly soluble in methanol.

ADRIAMYCIN Injection is a red coloured, clear solution and should be stored at 2°C - 8°C. ADRIAMYCIN Injection is available in vials containing the active ingredient doxorubicin hydrochloride 10 mg/5 mL, 20 mg/10 mL, 50 mg/25 mL and 200 mg/100 mL. The inactive ingredient is 0.9% saline solution.

PHARMACOLOGY

Though 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.

ADRIAMYCIN has immunosuppressive effects. It inhibits the titre of haemolytic and haemagglutinating antibodies in mice immunised with sheep red blood cells. Similar evidence in man indicates that ADRIAMYCIN is a powerful, but temporary immunosuppressant agent. ADRIAMYCIN is a cell cycle, phase non-specific cytotoxic drug.

The toxic effects of ADRIAMYCIN on the bone marrow appear to be related to its action on proliferating myeloid cells. The cardiotoxicity of ADRIAMYCIN is probably mediated by different mechanisms. Although, in animal systems, ADRIAMYCIN does inhibit DNA synthesis in cardiac muscle, it is probable that cardiotoxicity is not directly related to inhibition of cardiac muscle replication. There are some data which suggest that it is due to the generation of free radicals which damage cardiac muscle in some uncertain way. These data also suggest that concurrent administration of Vitamin E and other free radical acceptors may prevent cardiotoxicity in experimental animal systems without impairing its antitumour efficacy. These studies need confirmation but they do suggest that it may be possible to divorce the antitumour effects of the drug from its cumulative cardiotoxic effects.

The specificity of ADRIAMYCIN 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.

Pharmacokinetics

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

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

The metabolism and disposition of ADRIAMYCIN is still to be defined. The drug is metabolised predominantly by the liver to adriamycinol 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 ADRIAMYCIN 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, as determined by fluorimetric methods, accounts for approximately 4-5% of the administered dose in five days. Biliary excretion represents the major excretion route, 40-50% of the administered dose being recovered in the bile or the faeces in seven days. Impairment of liver function results in slower excretion, and consequently, increased retention and accumulation in plasma and tissues. ADRIAMYCIN does not cross the blood brain barrier.

**INDICATIONS**

ADRIAMYCIN has been used successfully to produce regression in neoplastic conditions such as: acute leukaemia, Wilms' tumour, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, lymphomas of both Hodgkin's and non-Hodgkin's type, bronchogenic (lung) carcinoma, thyroid carcinoma, hepatomas, ovarian carcinoma, etc. The main antitumour activities are listed in Table 1. ADRIAMYCIN is also indicated by intravesical administration in the primary management of non-metastatic carcinoma of the bladder. (Tis, T1, T2).
TABLE 1

ADRIAMYCIN ANTITUMOUR ACTIVITY

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Response Rate (%)</th>
<th>Median Duration (month)</th>
<th>First line Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established Activity</td>
<td>Breast</td>
<td>35</td>
<td>3-6</td>
</tr>
<tr>
<td></td>
<td>Ovary</td>
<td>38</td>
<td>3-6</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sarcoma</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Wilms'</td>
<td>66</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Bladder</td>
<td>28</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td>Neuroblastoma</td>
<td>41</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Hodgkin's</td>
<td>36</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin's Lymphoma</td>
<td>40</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td>Acute Leukaemia</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Hepatoma</td>
<td>32</td>
<td>4-6</td>
</tr>
<tr>
<td></td>
<td>Thyroid</td>
<td>30</td>
<td>6-10</td>
</tr>
<tr>
<td>Some Response</td>
<td>Stomach</td>
<td>30</td>
<td>2-4</td>
</tr>
<tr>
<td></td>
<td>Cervix</td>
<td>32</td>
<td>2-6</td>
</tr>
<tr>
<td></td>
<td>Head &amp; Neck</td>
<td>19</td>
<td>2-4</td>
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<tr>
<td></td>
<td>Testicle</td>
<td>20</td>
<td>3-6</td>
</tr>
<tr>
<td></td>
<td>Myeloma</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Endometrial</td>
<td>36</td>
<td>4-6</td>
</tr>
<tr>
<td>Unresponsive</td>
<td>Colorectal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Renal</td>
<td></td>
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<tr>
<td></td>
<td>Melanoma</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Brain</td>
<td></td>
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</tr>
</tbody>
</table>

CONTRAINDICATIONS

ADRIAMYCIN therapy should not be started in patients who have marked myelosuppression or severe stomatitis induced by previous treatment with other antitumour agents or by radiotherapy. Situations in which patients should not be treated with i.v. ADRIAMYCIN include patients with severe arrhythmias, myocardial insufficiency, myocardial infarction. ADRIAMYCIN treatment is contraindicated in patients who have previously received treatment with full cumulative doses of ADRIAMYCIN and Daunorubicin.

ADRIAMYCIN therapy is also contraindicated in patients with marked liver impairment, in pregnancy and lactation (see PRECAUTIONS), in the presence of generalised infection, and in patients with hypersensitivity to ADRIAMYCIN and/or other anthracyclines or anthracenediones.

Contraindications for intravesical use are:

- invasive tumours that have penetrated the bladder wall.

- urinary infections.
- inflammation of the bladder.
- catheterisation of the bladder (e.g. due to massive intravesical tumours).
- haematuria

PRECAUTIONS

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

ADRIAMYCIN is not an antimicrobial agent.

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

Initial treatment with ADRIAMYCIN 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. Blood count and liver function tests should be carried out prior to each ADRIAMYCIN treatment.

ADRIAMYCIN solution should be handled with care. If either of the preparations comes in contact with the skin or mucosae, the appropriate areas should be washed thoroughly with soap and water.

Cardiac Function
Special attention must be given to the cardiac toxicity exhibited by ADRIAMYCIN. Although uncommon, acute left ventricular failure has occurred, particularly in patients who have received total dosage of the drug exceeding the currently recommended limit of 550 mg/m². For this reason, cardiac function should be assessed before undergoing treatment with ADRIAMYCIN and has to be carefully monitored throughout therapy to minimise the risk of incurring severe cardiac impairment.

Cardiac failure is often not favourably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of drug induced heart failure appears to be essential for successful treatment with digitalis, diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent ECG changes. An assessment of cardiac function during ADRIAMYCIN treatment should also include the evaluation of the left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) or by multigated radionucleotide angiography (MUGA) scan, as well as ECG monitoring.

Baseline ECG and periodic follow-up ECG during, and immediately after drug therapy is an advisable precaution. Transient ECG changes, such as T-wave flattening, S-T
depression and arrhythmias are not considered indications for suspension of ADRIAMYCIN therapy. A persistent reduction in the voltage of the QRS wave is presently considered more specifically predictive for cardiac toxicity. If this occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

A decrease of the LVEF is the most predictive event related to chronic, cumulative dose-dependent cardiomyopathy. When a pre-treatment (baseline) assessment of LVEF is available, this parameter can be used as an indicator of cardiac function throughout therapy.

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.

As a general rule, in patients with normal baseline LVEF (\(\geq 50\%\)), an absolute decrease of \(\geq 10\%\) or a decline below the 50% threshold level are indicative of a deterioration of cardiac function and the continuation of doxorubicin treatment under such conditions has to be carefully evaluated. The probability of developing impaired myocardial function based on a combined index of signs, symptoms and a decline in LVEF can be estimated to be around 1-2% at a cumulative dose of 300 mg/m\(^2\); this probability will slowly increase up to the total cumulative dose of 450-550 mg/m\(^2\). Thereafter, the risk of developing CHF increases more steeply, and it is recommended not to exceed the total cumulative dose of 550 mg/m\(^2\).

If any additional risk factor for cardiac toxicity is present, cardiac toxicity might occur at lower cumulative doses and the monitoring of cardiac function must be particularly strict. 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. 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 approximately 28.5 days and may persist in the circulation for up to 24 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 24 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

ADRIAMYCIN induced cardiotoxicity mostly develops during the course of therapy up to two months from its termination but late events (several months to years after treatment termination) have occurred. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, 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.

For patients who have had mediastinal irradiation, concurrent high dose cyclophosphamide or hypertensive cardiomegaly it is recommended that the cumulative total lifetime dose of ADRIAMYCIN (including related drugs such as Daunorubicin) be less than 450 mg/m$^2$ body surface area. Congestive heart failure and/or cardiomyopathy may be encountered several weeks after discontinuation of ADRIAMYCIN therapy.

**Hematologic Toxicity**

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 ADRIAMYCIN. Red blood cell and platelet levels should also be monitored since they may also be depressed. Haematologic toxicity may require dose reduction, or suspension, or delay of ADRIAMYCIN therapy.

When using ADRIAMYCIN as part of chemotherapy regimens which combine drugs of similar pharmacological effects (i.e. cytotoxicity) additive toxicity is likely to occur. Such additive toxicity has to be taken into consideration especially with regard to bone marrow function.

ADRIAMYCIN is a powerful but temporary immunosuppressant agent. Appropriate measures should be taken to prevent secondary infection. Persistent severe myelosuppression may result in superinfection or haemorrhage.

**Hepatic Function**

Toxicity to recommended doses of ADRIAMYCIN is enhanced by hepatic impairment, therefore, prior to the individual dosing, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as AST (SGOT), ALT (SGPT), alkaline phosphatase, bilirubin and BSP. (see DOSAGE AND ADMINISTRATION). Lower doses are recommended in these patients (see DOSAGE AND ADMINISTRATION).

Changes in hepatic function induced by concomitant therapies, either given to achieve optimal antitumour efficacy or given for the pharmacological management of concomitant diseases, may affect ADRIAMYCIN metabolism, pharmacokinetics, therapeutic efficacy or toxicity.

**Obesity**

The systemic clearance of ADRIAMYCIN has been found to be reduced in obese patients; such patients have to be carefully monitored if undergoing treatment with the maximum recommended doses of the drug.
Extravasation and Rate of Administration

On intravenous administration of ADRIAMYCIN, 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.

The rate of administration is dependent on the size of the vein and the dosage. It is important that the dose be administered in not less than 3-4 minutes. 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.

Use in Intravesical Administration

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

Tumor-Lysis Syndrome

Like other cytotoxic drugs, ADRIAMYCIN may induce hyperuricaemia secondary to rapid lysis of neoplastic cells (tumor-lysis syndrome). The clinician should monitor the patient's blood uric acid level, potassium, calcium phosphate and creatinine, and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem. Hydration, urine alkalinisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimise potential complications of tumor-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.

Other

It has been reported that ADRIAMYCIN 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. Radiation-induced toxicities (myocardium, mucosae, skin and liver) have also 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.

ADRIAMYCIN imparts a red colouration to the urine for 1-2 days after administration and patients should be advised to expect this during active therapy.
Carcinogenicity, Mutagenicity and Impairment of Fertility

ADRIAMYCIN and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models.

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.

ADRIAMYCIN may cause infertility during the time of drug administration. In women, ADRIAMYCIN may cause amenorrhea. Although ovulation and menstruation appear to return after termination of therapy, 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.

ADRIAMYCIN 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 ADRIAMYCIN treatment should use effective contraceptive measures.

Use in Pregnancy - Category D

There is no information on the drug’s use in pregnancy; therefore, the drug should not be used in pregnant women or those likely to become pregnant unless the expected benefit outweighs any potential risk.

Although animal studies have not demonstrated teratogenic activity due to ADRIAMYCIN treatment, an embryotoxic action is evident. Studies with rabbits and rats have revealed a decreased weight gain and a higher incidence of resorbed foetuses. No greater incidence of gross, visceral or skeletal malformations or of post-natal deaths has been observed.

Dose-related mutagenic effects of ADRIAMYCIN have been reported to produce severe chromosomal aberrations in *in vitro* studies. In view of this activity, the use of this drug in pregnant women is not recommended.

Use in Lactation

ADRIAMYCIN is secreted in breast milk. ADRIAMYCIN treated women should be instructed not to breast-feed, given the potential for serious adverse reactions in nursing infants.

Instructions to be given to Patients

1. Patients should inform their physicians immediately if pain develops at the injection site.
2. Nausea and vomiting may be expected 3-6 hours after drug treatment, and may last for several hours.
3. Patients should be advised to expect a red colouration to the urine (not indicative of haematuria) for 1 to 2 days after each administration of ADRIAMYCIN.

4. Alopecia (hair loss) should be expected 1 to 2 weeks after the initiation of ADRIAMYCIN treatment. Hair loss may be complete but hair always returns after termination of treatment.

NB. Scalp tourniquets inflated to above systolic blood pressure and left in situ for 30 minutes over the time of ADRIAMYCIN treatment reduces the probability of alopecia.

5. Anorexia may be expected for 24 hours following each treatment and occasionally may persist for several days.

6. Hyperpigmentation, usually in the hands, nails and buccal mucosa may develop in patients receiving ADRIAMYCIN. Patients should be advised that this condition does not usually improve after termination of treatment.

7. Infertility in both sexes is usual in patients receiving ADRIAMYCIN. Amenorrhoea is frequent and in premenopausal women, regular menstruation usually returns a few months after termination of ADRIAMYCIN therapy. This is often accompanied by normal fertility.

Male patients should be advised that oligospermia or azoospermia may be permanent. There is a possibility that fertility may return several years after ceasing therapy. Men undergoing ADRIAMYCIN therapy should be advised to use effective contraceptive measures.

8. Patients should be instructed to inform their physicians of any prior abnormal heart or liver conditions, as this information is vital to the formulation of appropriate dosage regimes.

INTERACTIONS WITH OTHER MEDICINES

- Cyclophosphamide: Concurrent cyclophosphamide treatment sensitises the heart to the cardiotoxic effects of ADRIAMYCIN (see WARNINGS). ADRIAMYCIN may exacerbate cyclophosphamide cystitis.

- Heparin: ADRIAMYCIN should not be mixed with heparin since it has been reported that these drugs are incompatible to the extent that a precipitate may form.

- Adjuvant Chemotherapy involving ADRIAMYCIN: It is not recommended that ADRIAMYCIN be used routinely as adjuvant chemotherapy in any tumour category. The activity of ADRIAMYCIN in combination with other drugs is affected not only by the nature of the drug itself, but also by the schedule of administration. It is strongly recommended that in situations where ADRIAMYCIN is intended for use as adjuvant chemotherapy, higher authorities as well as the Hospital Ethical Committee be consulted.
• Propranolol: In view of the finding that ADRIAMYCIN and propranolol have both been shown to inhibit cardiac mitochondrial CoQ10 enzymes it is possible that such a drug interaction may result in an additive cardiotoxic effect.

• 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.

• Radiotherapy: Concurrent radiotherapy and ADRIAMYCIN treatment may be associated with increased radiation toxicity, i.e. skin reactions and mucositis.

• Mediastinal Radiotherapy: Concurrent mediastinal radiotherapy and ADRIAMYCIN may be associated with enhanced myocardial toxicity of ADRIAMYCIN (see WARNINGS).

• 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 a major substrate of cytochrome P450 CYP3A4 and CYP2D6, and P-glycoprotein (P-gp). 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 hematologic toxicity than that observed with doxorubicin alone. Coma and seizures have also been described with concomitant administration of cyclosporine and doxorubicin.

**ADVERSE EFFECTS**

**More Common Reactions**

Cardiovascular: Cardiotoxicity, i.e. cardiomyopathy, congestive heart failure.

Dermatological: ADRIAMYCIN extravasation, skin necrosis, cellulitis, vesication, local phlebitis, thrombophlebitis, reversible alopecia, erythematous streaking along the vein proximal to the site of injection, phlebosclerosis.

Gastrointestinal: Nausea and vomiting, mucositis (stomatitis and oesophagitis), diarrhoea, abdominal pain.

General: Dehydration, facial flushing (if an injection has been given too rapidly).
Haematological: Myelosuppression, leucopenia, haemorrhage.

**Less Common Reactions**

Dermatological: Urticarial rash, hyperpigmentation of nailbeds and dermal creases (primarily in children in a few cases), recall of skin reaction due to prior radiotherapy, acral erythema, palmar plantar erythrodysaesthesia.

General: Chills and fever, anorexia, anaphylaxis.

Haematological: Thrombocytopenia, anaemia, febrile neutropenia, septicemia, and death.

Liver: Changes in transaminase levels.

Nervous system: Drowsiness.

Ocular: Conjunctivitis, lacrimation.

Renal: Renal damage, hyperuricaemia.

Cardiovascular: Pericardial effusions, thromboembolism.

Gastrointestinal: Bleeding, ulceration and necrosis of the colonic mucosa have occurred in patients with acute myelogenous leukemia treated with the combination of doxorubicin and cytarabine.

Other: Amenorrhoea, azoospermia, hot flushes, malaise/asthenia, shock.

**Serious or Life-Threatening Reactions**

Myelosuppression: This accompanies effective ADRIAMYCIN treatment in almost 100% of patients. Leucopenia is the predominant effect with thrombocytopenia and anaemia occurring less frequently. 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 (see DOSAGE AND ADMINISTRATION) and simultaneous treatment with other myelosuppressive agents. The nadir (time from treatment to peripheral blood evidence of maximal myelosuppression) of leucopenia and thrombocytopenia is 10 to 15 days after treatment, and counts return to normal before day 21.

Other Haematological: The occurrence of secondary acute myeloid leukaemia with or without a pre-leukaemic phase has been reported in patients concurrently treated with doxorubicin in association with DNA-damaging antineoplastic agents. Secondary leukemia 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. This has been noted in the adjuvant and neoadjuvant setting. Such cases may have a short (1-3 year) latency period.
Mucositis: This phenomenon is a frequent and painful complication of ADRIAMYCIN treatment but is less common than myelosuppression. Mucositis most commonly develops 5 to 10 days after treatment, and typically begins as a burning sensation in the mouth and pharynx. The mucositis may involve the vagina, rectum and oesophagus, and progress to ulceration with risk of secondary infection. The mucositis usually subsides in 10 days. Retrospective comparison of the incidence of mucositis suggests that it is less frequent as the intervals between doses increase. Mucositis may be severe in patients who have had previous irradiation to the mucosae.

Cardiotoxicity: The cardiac abnormalities caused by ADRIAMYCIN treatment can be separated into two categories:

i) ECG alterations; and

ii) Congestive heart failure.

ECG changes following ADRIAMYCIN treatment occur in about 10% of patients at all dose levels of ADRIAMYCIN, are usually reversible and do not appear to be related to the subsequent development of congestive cardiac failure.

The total (cumulative) dose levels of ADRIAMYCIN do correlate with the incidence of drug induced congestive cardiac failure (cardiomyopathy). Limitation of the total dose of ADRIAMYCIN to 500 mg/m² reduces the risk of drug induced cardiomyopathy. At the cellular level, ADRIAMYCIN induced cardiotoxicity is due to myocyte damage. Furthermore, as a consequence of the inhibition of cellular proliferation not only of neoplastic cells but also normal cells, cardiac muscle cells are unable to regenerate.

Microscopical examination of endocardial biopsies shows two major types of myocyte damage:

1. Cells totally or partially devoid of myofibrillar content, even though the nucleus and mitochondria are intact;

2. Vacuolar degeneration.

Damage to the myocardial muscle occurs with very little inflammatory reaction, muscle fibres appear to fade away. The clinical spectrum of ADRIAMYCIN toxicity ranges from subtle changes in ventricular function that can be detected only by sophisticated studies to gross congestive cardiomyopathy with symptoms and signs of advanced congestive heart failure.

The following measures may identify patients with early ADRIAMYCIN cardiomyopathy: progressive flattening or inversion of the T-waves (mainly in the left precordial leads), low QRS voltage, prolonged systolic time interval, reduced ejection fraction (echocardiography or by cardiac pool scanning) or cardiac biopsy showing characteristic electromicroscopic changes. ADRIAMYCIN cardiomyopathy is frequently fatal. If diagnosed early, management with digoxin, diuretics and bed rest may control the heart failure.

Animal studies have indicated a possible relationship between the inhibition by ADRIAMYCIN of the mitochondrial biosynthesis of Coenzyme Q 10 and
ADRIAMYCIN induced cardiotoxicity. Other studies have suggested that Vitamin E and other free radical acceptors may prevent ADRIAMYCIN toxicity.

**Intravesical use**

Systemic toxicity is not a common problem, however, adverse reactions have been noted at doses exceeding that recommended (see DOSAGE AND ADMINISTRATION).

Local reactions observed include chemical cystitis, contraction of the bladder, haematuria, painful micturition, frequency and urgency. These disturbances are transient. Special attention is required for catherisation problems (e.g., urethral obstruction due to massive intravesical tumours.).

**DOSAGE AND ADMINISTRATION**

Care in the administration of ADRIAMYCIN will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. The recommended dosage schedule is 60-75 mg/m\(^2\) as a single intravenous injection administered at 21 day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration. An alternative dose schedule is 30 mg/m\(^2\) on each of three successive days repeated every 4 weeks. The adult dosage regimens may be suitable for paediatric cases. The recommended lifetime cumulative dose limit is 550 mg ADRIAMYCIN/m\(^2\) body surface area. ADRIAMYCIN has been administered as an intra-arterial infusion for 1-3 days at doses of 45-100 mg/m\(^2\). It is recommended that the total cumulative dose of ADRIAMYCIN for adults aged 70 or older be restricted to 450 mg/m\(^2\) body surface area.

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

<table>
<thead>
<tr>
<th>Serum Bilirubin Levels</th>
<th>BSP Retention</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 – 50 µmol/L</td>
<td>9 - 15%</td>
<td>1/2 normal dose</td>
</tr>
<tr>
<td>&gt; 50 µmol/L</td>
<td>&gt; 15%</td>
<td>1/4 normal dose</td>
</tr>
</tbody>
</table>

ADRIAMYCIN Injection is supplied as 10 mg, 20 mg, 50 mg and 200 mg doxorubicin hydrochloride in 5, 10, 25 and 100 mL vials, respectively (doxorubicin concentration 2 mg/mL). The 100 mL vial size is a hospital pharmacy bulk pack intended for multidose dispensing.

ADRIAMYCIN Injection must be handled with care. If contact with the skin occurs, wash thoroughly with soap and water. The product contains no antimicrobial preservative. The single dose vials should be used in one patient on one occasion only. Discard any residue. The solution is to be stored under refrigeration (2-8°C) and should be protected from sunlight and retained in the carton until time of use.
The 100 mL vial is for use on one occasion for multi-dose dispensing only and any residue should be discarded. Dispensed solutions should be used as soon as practicable, otherwise store at 2°C to 8°C (Refrigerate. Do not freeze) and use within 24 hours.

Storage of ADRIAMYCIN 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 room temperature (15 - 25 °C).

It is recommended that ADRIAMYCIN be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection U.S.P. or 5% Glucose Injection U.S.P. 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 3-5 minutes. 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.

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.

Until specific compatibility data are available, it is not recommended that ADRIAMYCIN be mixed with other drugs. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin. ADRIAMYCIN 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 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.

ADRIAMYCIN has been used in combination with other approved chemotherapeutic agents.

Though evidence is available that at least in some types of neoplastic disease combination chemotherapy is superior to single agents the benefits and risks of such therapy have not yet been fully elucidated.
**Intravesical administration**

The following procedure is recommended:

1. The bladder should be catheterised and emptied.

2. Dilute ADRIAMYCIN to a final concentration of 80 mg in 100 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 alternate to the opposite side over a 1 hour period.

4. The patient should be requested not to urinate for 1 hour, after which the bladder should be emptied of solution.

5. The procedure should be repeated at monthly intervals.

**Protective measures**

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

- Personnel should be trained in good technique for reconstitution 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 reconstitution, 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.
OVERDOSAGE

Acute overdose with doxorubicin will result in acute cardiac alterations, severe myelosuppression (mainly leukopenia and thrombocytopenia), and gastrointestinal toxic effects (mainly mucositis).

Delayed cardiac failure may occur up to six months after the overdosage. Patients should be observed carefully and should signs of cardiac failure arise, be treated along conventional lines.

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 myelosupression, the effects of which are greatest between 10 and 15 days after administration.

Toxic blood levels have not been established. Doxorubicin is highly protein bound, however, if haemoperfusion is initiated within minutes of an overdose, a reduction in serum levels can be achieved. Haemodialysis is unlikely to be effective.

There is no specific antidote for doxorubicin. Symptomatic supportive measures should be instituted. Support respiratory and cardiac function. Cardiac monitoring is recommended. Particular attention should be given to prevention and treatment of possible severe haemorrhages or infections secondary to severe, persistent bone marrow depression.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

ADRIAMYCIN Injection is available supplied in vials containing:

10 mg of doxorubicin hydrochloride in 5 mL of 0.9% saline solution. Supplied as a single vial.

20 mg of doxorubicin hydrochloride in 10 mL of 0.9% saline solution. Supplied as a single vial.

50 mg of doxorubicin hydrochloride in 25 mL of 0.9% saline solution. Supplied as a single vial.

200 mg of doxorubicin hydrochloride in 100 mL of 0.9% saline solution. Supplied as a single vial. (pharmacy bulk pack for multi-dose use in a hospital only)

Refrigerate. Store at 2°C - 8°C.

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – prescription only
NAME AND ADDRESS OF SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114
Australia

DATE OF TGA APPROVAL: 29 January 2007

DATE OF MOST RECENT AMENDMENT: 5 June 2012

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