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ROBOL

Doxorubicin Concentrate for Solution for Infusion 2 mg/ml

For Intravenous and Intravesical Use

NAME OF THE MEDICINE
ROBOL (Doxorubicin Concentrate for Solution for Infusion 2 mg/ml)

QUALITATIVE AND QUANTITATIVE COMPOSITION
ROBOL is available in vials containing the active ingredient doxorubicin hydrochloride.
Doxorubicin hydrochloride is a red-orange, hygroscopic crystalline powder that is soluble in water and in isotonic sodium chloride solution. Slightly soluble in methanol. Practically insoluble in chloroform, in ether and in other organic solvents.
Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of Streptomyces peucetius var. caesius.

PHARMACEUTICAL FORM
ROBOL (DOXORUBICIN CONCENTRATE FOR SOLUTION FOR INFUSION 2 MG/ML), is a red solution free from visible extraneous particulate matter.
Each 1 ml contains 2 mg Doxorubicin hydrochloride.
After reconstitution: A light red solution.

CLINICAL PARTICULARS
Therapeutic indications: ROBOL 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. Doxorubicin is also indicated by intravesical administration in the primary management of non-metastatic carcinoma of the bladder (Tis, T1, T2).
Doxorubicin has some antitumour activities against stomach, cervix, head and neck, testicle, myeloma and endometrial cancer.

DOSE AND METHOD OF ADMINISTRATION
Dosage: Care in the administration of ROBOL 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 doxorubicin/m^2 body surface area. ROBOL 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 doxorubicin for adults aged 70 or older be restricted to 450 mg/m^2 body surface area.

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

Serum Bilirubin Levels	BSP Retention	Recommended Dose
20 – 50 μmol/L	9 - 15%	1/2 normal dose
> 50 μmol/L	> 15%	1/4 normal dose

METHOD OF ADMINISTRATION
ROBOL Injection is supplied as 10 mg doxorubicin hydrochloride in 5 mL vials, 50 mg doxorubicin hydrochloride in 25 mL vials and 200 mg doxorubicin hydrochloride in 100 mL vials respectively (doxorubicin concentration 2 mg/mL).
Doxorubicin 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°C to 8°C) and should be protected from sunlight and retained in the carton until time of use.
Storage of Doxorubicin 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 (20°C to 25°C).
It is recommended that Doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection. or 5% Glucose Injection. 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 Doxorubicin 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 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 administrations of these drugs.
Doxorubicin 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.

Doxorubicin must not be given intrathecally or intramuscularly or by long-term infusion. Direct intravenous infusion is not advised due to the tissue damage that may occur if the infusion infiltrates the tissues. If a central vein catheter is used then infusion of doxorubicin in sodium chloride 0.9 % injection is advised.

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.

METHOD OF ADMINISTRATION
Intravesical Administration:
The following procedure is recommended:
- The bladder should be catheterised and emptied.
- Dilute ROBOL to a final concentration of 80 mg in 100 mL of normal saline and instil via the catheter into the bladder.
- 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.
- The patient should be requested not to urinate for 1 hour, after which the bladder should be emptied of solution.The procedure should be repeated at monthly intervals.

Route of Administration: Intravenous and Intravesical

CONTRAINDICATIONS
- Hypersensitivity to doxorubicin or any other component of the product, other anthracyclines or anthracenediones.
- Pregnancy and lactation (see section Special warnings and precautions for use).

Contraindications for intravenous (IV) use:
- persistent myelosuppression or severe stomatitis induced by previous treatment with other antitumour agents or by radiotherapy;
- presence of generalised infection;
- severe arrhythmias;
- severe myocardial insufficiency;
- recent myocardial infarction;
- severe liver impairment;
- previous treatment with maximum cumulative doses of doxorubicin, daunorubicin, epirubicin, idarubicin and/or other anthracyclines and anthracenediones (see Section Special warnings and precautions for use).

Contraindications for intravesical use:
- 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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
CAUTION: Cytotoxic Agent: It is dangerous to take this preparation except under Medical Supervision.

General: ROBOL should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. ROBOL 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 ROBOL. Initial treatment with ROBOL 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 ROBOL treatment.
ROBOL solution should be handled with care. If either of the preparations comes in contact with the skin or mucosa, the appropriate areas should be washed thoroughly with soap and water.

WARNINGS
- For intravenous or intravesical use only. Severe local tissue necrosis will occur if there is extravasation during administration. Doxorubicin must not be given by the intramuscular or subcutaneous route.
- Serious irreversible myocardial toxicity with delayed congestive failure often unresponsive to any cardiac supportive therapy may be encountered as total dosage approaches 550 mg/m^2.
- This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy.
- Dosage should be reduced in patients with impaired hepatic function.
- Severe myelosuppression may occur.

Cardiac Function: Special attention must be given to the cardiac toxicity exhibited by doxorubicin. Cardiotoxicity is a risk of anthracycline treatment that may be manifested by early (i.e., acute) or late (i.e., delayed) events. The cardiac abnormalities caused by treatment can be separated into 2 categories:

1. ECG alterations and
2. Congestive heart failure (CHF)

Early (i.e., Acute) Events: Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions, ventricular tachycardia and 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 the discontinuation of doxorubicin treatment. ECG changes following doxorubicin treatment occur in about 10% of patients at all dose levels of doxorubicin, are usually reversible and do not appear to be related to the subsequent development of congestive cardiac failure.

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.

The following measures may identify patients with early 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. Cardiomyopathy induced by doxorubicin is frequently fatal. 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.
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/m^2. For this reason, cardiac function should be assessed before patients undergo treatment with doxorubicin and must be carefully 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. Severe cardiac toxicity may occur precipitously without antecedent ECG changes.
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 doxorubicin 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 (≥50%), an absolute decrease of ≥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 slowly increases 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.
Cardiac function must be carefully monitored in patients receiving high cumulative doses and in those with risk factors. However, cardiac toxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present.
Risk factors for cardiac toxicity include active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with anthracyclines or anthracenediones, concomitant use of drugs with the ability to suppress cardiac contractility or 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 Interactions with other medicines and other forms of interactions). Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as e.g. trastuzumab (variable half-life; washout period up to 7 months), may also be at an increased risk of

developing cardiotoxicity.
Note: Trastuzumab emtansine has a shorter half-life of approximately 4 days. 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.
For patients who have had mediastinal irradiation, concurrent high dose cyclophosphamide or hypertensive cardiomegaly it is recommended that the cumulative total lifetime dose of doxorubicin (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 doxorubicin therapy.
The total (cumulative) dose levels of doxorubicin correlate with the incidence of drug induced congestive cardiac failure (cardiomyopathy). Limitation of the total dose of doxorubicin to 500 mg/m^2 reduces the risk of drug induced cardiomyopathy. At the cellular level, cardiotoxicity induced by doxorubicin 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 doxorubicin 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.
It is probable that the toxicity of doxorubicin and other anthracyclines or anthracenediones is additive.
Animal studies have indicated a possible relationship between the inhibition by doxorubicin of the mitochondrial biosynthesis of Coenzyme Q 10 and cardiotoxicity induced by doxorubicin. Other studies have suggested that Vitamin E and other free radical acceptors may prevent doxorubicin toxicity.

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 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 are generally more severe with high-dose schedules, reaching the nadir in most cases between days 10-14 after drug administration; this is usually transient with the WBC/neutrophil counts returning to normal values in most cases by day 21. White blood cell counts as low as $1000/mm^3$ are to be expected during treatment with appropriate doses of doxorubicin.
Myelosuppression accompanies effective doxorubicin treatment in almost 100% of patients. Leucopenia is the predominant effect with thrombocytopenia and anaemia occurring less frequently. Red blood cell and platelet levels should also be monitored.
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 Dose and method of administration) and simultaneous treatment with other myelosuppressive agents. Haematologic toxicity may require dose reduction, suspension or delay of ROBOL therapy.
When using doxorubicin 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.
Doxorubicin is a powerful but temporary immunosuppressant agent. Appropriate measures should be taken to prevent secondary infection. Clinical consequences of severe myelosuppression include fever, infection, sepsis/septicaemia, septic shock, haemorrhage, tissue hypoxia or death.

Secondary Leukaemia: Secondary leukaemia, with or without a pre-leukaemic 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, when patients have been heavily pre-treated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. This has been noted in the adjuvant and neoadjuvant setting. These leukaemias can have a 1 to 3 year latency period.

Gastrointestinal: Doxorubicin is emetogenic. Mucositis is a frequent and painful complication of doxorubicin treatment but is less common than myelosuppression. Mucositis/stomatitis generally appears early after drug administration, most commonly developing 5 to 10 days after treatment. It typically begins as a burning sensation in the mouth and pharynx. The mucositis may involve the vagina, rectum and oesophagus, and, if severe, may progress over a few days to mucosal ulcerations with risk of secondary infection. Most patients recover from this adverse event by the 3^{rd} week of therapy. 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.

Obesity: The systemic clearance of doxorubicin 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.

Effects at Site of Injection: Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimise the risk of phlebitis/thrombophlebitis at the injection site (Dose and method of administration).

Extravasation: Extravasation of doxorubicin during intravenous injection may produce local pain (a burning or stinging sensation), severe tissue lesions (vesication, severe cellulitis) and necrosis. Should signs or symptoms of extravasation occur during intravenous administration of doxorubicin, the drug infusion should be immediately stopped. To minimise perivenous infiltration, see Dose and method of administration.

Tumour-Lysis Syndrome: Like other cytotoxic drugs, doxorubicin may induce hyperuricaemia as a consequence of the extensive purine catabolism that accompanies rapid drug-induced lysis of neoplastic cells (tumour-lysis syndrome). The clinician should monitor the patient's blood uric acid level, potassium,calcium phosphate and creatinine. Supportive and pharmacologic measures should be used to control this problem. 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.

Other: Doxorubicin may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide induced haemorrhagic cystitis, mucositis induced by radiotherapy, and enhanced hepatotoxicity of 6-mercaptopurine have been reported. 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.
Doxorubicin imparts a red colouration to the urine for 1-2 days after administration and patients should be advised to expect this during active therapy.

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

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 ROBOL.
4. Alopecia (hair loss) should be expected 1 to 2 weeks after the initiation of ROBOL 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 Doxorubicin 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 ROBOL. 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 Doxorubicin. Amenorrhoea is frequent and in pre-menopausal women, regular menstruation usually returns a few months after termination of ROBOL therapy. This is often accompanied by normal fertility.
8. 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 ROBOL therapy should be advised to use effective contraceptive measures.
9. 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.

Use in Hepatic Impairment: The major route of elimination of doxorubicin is the hepatobiliary system. Toxicity to recommended doses of doxorubicin 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 Dose and method of administration). Serum total bilirubin levels should also be evaluated 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 (Dose and method of administration). Patients with severe hepatic impairment should not receive doxorubicin (see Contraindications).
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 doxorubicin metabolism, pharmacokinetics, therapeutic efficacy or toxicity

Use in the Elderly: No data available.

Paediatric Use: No data available.

Effects on Laboratory Tests: No data available.

Interactions with other medicines and other forms of interactions: 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.
Doxorubicin is mainly used in combination with other cytotoxic agents. Additive toxicity may occur, especially with regard to bone marrow/haematologic and gastrointestinal effects (see Special warnings and precautions for use).

Adjuvant Chemotherapy Involving Doxorubicin: It is not recommended that doxorubicin be used routinely as adjuvant chemotherapy in any tumour category. The activity of doxorubicin 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 doxorubicin is intended for use as adjuvant chemotherapy, higher authorities as well as the Hospital Ethical Committee be consulted.

Cyclophosphamide: Concurrent cyclophosphamide treatment sensitises the heart to the cardiotoxic effects of doxorubicin (see Section 4.4 Special warnings and precautions for use). Doxorubicin may exacerbate cyclophosphamide cystitis.

Cyclosporin: The addition of cyclosporin 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 cyclosporin 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 cyclosporin and doxorubicin.

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

Mediastinal Radiotherapy: Concurrent mediastinal radiotherapy and doxorubicin may be associated with enhanced myocardial toxicity of doxorubicin (see Special warnings and precautions for use).

Paclitaxel: 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.

Propranolol: In view of the finding that doxorubicin 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.

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

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.

FERTILITY, PREGNANCY AND LACTATION
Effects on Fertility: Doxorubicin may cause infertility during the time of drug administration. In women, doxorubicin 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.
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 treatment with doxorubicin should use effective contraceptive measures.

Use in Pregnancy: 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. 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. Although animal studies have not demonstrated teratogenic activity due to doxorubicin 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 doxorubicin 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: Doxorubicin is secreted in breast milk. Women should be instructed not to breast-feed while undergoing treatment with doxorubicin.

Effects on ability to drive and use machines: The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

Adverse effects (undesirable effects)
Adverse reactions reported in association with doxorubicin therapy are listed below by MedDRA System Organ Class. Frequencies are defined as: Very common, Common, Uncommon, Rare, Very rare and Not known.

Blood and Lymphatic System Disorders	
Very common	Leucopenia, neutropenia, anaemia, thrombocytopenia
Cardiac Disorders	
Common	Cardiomyopathy, congestive cardiac failure, sinus tachycardia
Not known	Atrioventricular block, tachyarrhythmia, bundle branch block, pericardial effusion
Eye Disorders	
Common	Conjunctivitis
Not known	Keratitis, increased lacrimation
Gastrointestinal Disorders	
Very common	Mucosal inflammation/stomatitis, diarrhoea, vomiting, nausea
Common	Oesophagitis, abdominal pain
Not known	Gastrointestinal haemorrhage, erosive gastritis, colitis, mucosal discolouration, large intestinal haemorrhage[a], gastrointestinal necrosis[a], large intestinal ulcer[a]
General Disorders and Administration Site Conditions	
Very common	Pyrexia, asthenia, chills
Common	Infusion site reaction, extravasation
Not known	Malaise, injection site erythema, death
Immune System Disorders	
Not known	Anaphylactic reaction
Infections and Infestations	
Very common	Infection
Common	Sepsis, cellulitis
Investigations	
Very common	Decreased ejection fraction, abnormal transaminases, increased weight, abnormal electrocardiogram
Metabolism and Nutrition Disorders	
Very common	Decreased appetite
Not known	Dehydration, Hyperuricaemia
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	
Not known	Acute lymphocytic leukaemia, acute myeloid leukaemia
Nervous System Disorders	
Not known	Somnolence
Renal and Urinary Disorders	
Not known	Chromaturia[c], renal disorder
Reproductive System and Breast Disorders	
Not known	Amenorrhoea, azoospermia, oligospermia
Skin and Subcutaneous Tissue Disorders	
Very common	Palmar-plantar erythrodysaesthesia syndrome, alopecia
Common	Urticaria, rash, skin hyperpigmentation, nail hyperpigmentation
Not known	Recall phenomenon, photosensitivity reaction, pruritus, skin disorder, skin necrosis, skin wrinkling, blister
Vascular Disorders	
Uncommon	Embolism
Not known	Shock, haemorrhage, thrombophlebitis, phlebitis, phlebosclerosis, hot flush, flushing
a. Reported in patients with acute myelogenous leukaemia treated with combination doxorubicin and cytarabine	
b. Reported in patients with early breast cancer receiving doxorubicin-containing adjuvant therapy	
c. For one to two days after administration	

Intravesical Use: Systemic toxicity is not a common problem, however, adverse reactions have been noted at doses exceeding that recommended (see Dose and method of administration).
Local reactions observed include chemical cystitis, contraction of the bladder, haematuria, painful micturition, frequency and urgency. These disturbances are transient.

OVERDOSAGE
Acute overdose with doxorubicin will result in acute cardiac alterations, severe myelosuppression (mainly leucopenia 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 myelosuppression, 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.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Mechanism of Action: 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.
Doxorubicin 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 doxorubicin is a powerful, but temporary immunosuppressant agent.
Doxorubicin is a cell cycle, phase non-specific cytotoxic drug.
The toxic effects of doxorubicin on the bone marrow appear to be related to its action on proliferating myeloid cells. The cardiotoxicity of doxorubicin is probably mediated by different mechanisms. Although, in animal systems, doxorubicin 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 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.

PHARMACOKINETIC PROPERTIES
Absorption/Distribution: ROBOL 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 ROBOL (doxorubicin hydrochloride) for injection is followed by rapid plasma clearance and significant tissue binding. No information on plasma-protein binding of doxorubicin is available. Doxorubicin does not cross the blood brain barrier.

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

Excretion: Urinary excretion, as determined by fluorimetric methods, accounts for approximately 4% to 5% of the administered dose in five days. Biliary excretion represents the major excretion route, 40% to 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.

PHARMACEUTICAL PARTICULARS
List of excipients:
Sodium chloride
Hydrochloric acid
Water for injections

Incompatibilities: Doxorubicin should not be mixed with heparin as a precipitate may form and it is not recommended that Doxorubicin be mixed with other drugs. 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 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 administrations of these drugs.

Shelf life
Unopened vial: 24 months

Reconstituted solution: Up to 7 days

Reconstituted solution: Doxorubicin hydrochloride Injection must be diluted prior infusion. Doxorubicin hydrochloride injection should be diluted with 0.9% Sodium Chloride Injection & 5% Dextrose Injection to a final concentration of 0.5 mg/ml for intravenous infusion and diluted with 0.9% Sodium Chloride Injection to a final concentration of 0.8mg/ml for intravesical administration. The solutions are physically and chemically stable for up to 7 days at room temperature (approximately 25°C) and refrigerated condition (2°C to 8°C).
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.

STORAGE CONDITION
Special precautions for storage: Unopened vials of ROBOL (DOXORUBICIN CONCENTRATE FOR SOLUTION FOR INFUSION 2 MG/ML) must be stored under refrigerated conditions between 2°C to 8°C. Discard unused portion. Protect from light. Keep out of reach of children.
Doxorubicin Injection diluted in 0.9% Sodium Chloride Injection or 5% Dextrose Injection is stable at room temperature (20°C - 25°C) and refrigerated condition (2°C to 8°C) for up to 7 days but the infusion must be completed within that time.

Nature and contents of container: ROBOL (Doxorubicin Concentrate For Solution For Infusion 2 mg/ml) is packed as 10 mg/5 ml in 5 ml Type-I tubular amber coloured glass vial with 5 mL nominal capacity with reinforced Non-PVC Base which are stoppered with 20 mm Type II Omniflex rubber plug and tampered with 20 mm aluminium flip off red seal top. One 5.0 ml tubular amber coloured glass vial packed in unit carton (without diluent). Each vial is packed into secondary carton along with a package insert.

ROBOL (Doxorubicin Concentrate For Solution For Infusion 2 mg/ml) is packed as 50 mg/25ml in Type-I moulded amber coloured glass vial with 30mL nominal capacity with reinforced Non-PVC Base which are stoppered with 20 mm Type II Omniflex rubber plug and tampered with 20 mm aluminium flip off red seal top. One 30.0 ml tubular amber coloured glass vial packed in unit carton (without diluent). Each vial is packed into secondary carton along with a package insert.

ROBOL (Doxorubicin Concentrate For Solution For Infusion 2 mg/ml) is packed as 200 mg/100 ml in Type-I moulded amber coloured glass vial with 100 mL nominal capacity with reinforced Non-PVC Base which are stoppered with 20 mm Type II Omniflex rubber plug and tampered with 20 mm aluminium flip off red seal top. One 100.0 ml tubular amber coloured glass vial packed in unit carton (without diluent). Each vial is packed into secondary carton along with a package insert.

Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

MAL No. : MAL22056054AZ

Product Registration Holder:
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53, Jalan Tembaga SD 5/2B, Bandar Sri
Damansara, 52200, Kuala Lumpur, Malaysia

Manufactured by :
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Hill Top Industrial Estate, Jharmajri, EPIP
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