metabolism, pharmacokinetics, therapeutic efficacy, and / or toxicity. Toxicities associated with DOXORUBA™, especially hematologic and gastrointestinal events, may be increased when Doxorubicin is used in combination with other cytotoxic drugs.

Paclitaxel: There have been number of reports in the literature that determine an increase in cardiotoxicity, when doxorubicin is co-administered with paclitaxel infused over 24 hours followed by doxorubicin administered over 48 hours resulted in a significant decrease in doxorubicin clearance with more profound neutropenic and stomatitis episodes than the reverse sequence of administration.

Progesterone: In a published study, progesterone was given intravenously to patients with advanced maligancies (ECOG PS < 2) at high dose (up to 10 g over 24 hours) concomitantly with a fixed doxorubicin dose (60 mg / m^2) via bolus injection. Enhanced doxorubicin induced neutropenia and thrombocytopenia was observed.

Cyclophosphamide: The addition of Cyclophosphamide to doxorubicin treatment does not affect exposure to doxorubicin, but many result in an increase in exposure to doxorubicinol, a metabolite. Doxorubicinol only has 5 % of the cytotoxic activity of doxorubicin. Concurrent treatment with doxorubicin has been reported to exacerbate Cyclophosphamide induced hemorragic cystitis. Acute myeloid leukemia has been reported as a second maligancy after treatment with doxorubicin and Cyclophosphamide.

OVERDOSAGE

Acute overdosage with doxorubicin enhances the toxic effect of mucositis, leukopenia and thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization antimicrobials, platelet transfusions and symptomatic treatment of muscositis. Use of hemopoietic growth factor (G-CSF, GM-CSF) may be considered. Cumulative dosage with doxorubicin increases the risk of cardiomyopathy and resultant congestive heart failure. Treatment consists of vigorous management of congestive heart failure with digitalis preparations, diuretics and after load reducers such as ACE inhibitors.

STORAGE

Store the vials in the original carton under refrigeration between 2 - 8 ^{o}C (36 - 46 ^{o}F). Protect from light.

PRESENTATION

DOXORUBA™ is available as 10 mg/5 ml and 50 mg/25 ml of Doxorubicin Hydrochloride respectively, as a ready to use solution.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all the procedures recommended in the guidelines are necessary or appropriate.

However, given the toxic nature of this substance, the following protective recommendations are provided:

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.

Caregivers of pediatric patients receiving doxorubicin should be counseled to take precautions (such as wearing latex gloves) to prevent contact with the patient's urine and other body fluids for at least 5 days after each treatment.

Marketed by:
Getwell Oncology Pvt. Ltd.
(A unit of Getwell)
464, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

Manufactured by:
Getwell Pharmaceuticals
474, Udyog Vihar, Phase-V, Gurgaon - 122016, Haryana, India

0700DDH

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Doxorubicin Hydrochloride Injection IP

DOXORUBA™

Cytotoxic Agent

FOR I.V INFUSION ONLY

Rx only

WARNING

General: Doxorubicin should be administered only under the supervision of a qualified. physician experienced in the use of cytotoxic therapy. Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with doxorubicin. Also initial treatment with doxorubicin should be preceded by a careful baseline assessment of blood counts; serum level of total bilirubin AST, and creatinine; and cardiac function as measured by Left Ventricular Ejection Function (LVFE). Patients should be carefully monitored during treatment for possible clinical complication due to myelosuppression. Supportive care may be necessary for the treatment of severe neutropenia and severe infectious complications. Monitoring for potential cardiotoxicity is also important, especially with greater cumulative exposure to doxorubicin. Doxorubicin may potentiate the toxicity of other anticancer therapies.

Secondary Leukemia: The occurrence of secondary AML or MDS has been reported most commonly in patients treated with chemotherapy regimens containing anthracyclines and DNA - damaging antineoplastic agents, in combination with radiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. Such cases generally have a 1 to 3 years latency period. The rate of developing secondary AML or MDS has been estimated in an analysis of 8563 patients with early breast cancer treated in 6 studies conduct by the National Surgical Adjuvant Breast and Bowel Project (NSABP), including (NSABP B 15). Patients in these studies received standard dose of doxorubicin and standard or escalated dose of Cyclophosphamide (AC) adjuvant chemotherapy and were followed for 61, 810 patient. Among 4483 such patients whoreceived conventional doses of AC, 11 cases of AML or MDS were identified, for an incidence of 0.32 years per 1000 patient years and cumulative incidence at 5 years of 0.21 % (95 % CI 0.11 - 0.41 %). In another analysis of 1474 patients with breast cancer who received adjuvant treatment with doxorubicin containing regimen in clinical trials conducted at University of Texas M.D. Anderson Cancer Centre, the incidence was estimated at 1.5 % at 10 years. In both experiences, patients who received regimens with higher Cyclophosphamide dosages, who received radiotherapy, or who were aged 50 or older had an increased risk of secondry AML or MDS. Pediatric patients are also at risk of developing secondary AML or MDS.

Pediatric patients are also at risk of developing secondary AML.

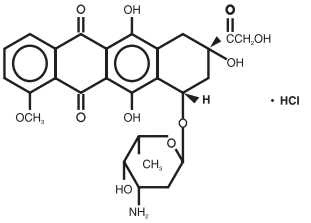
Cardiac Function: Cardiotoxicity is a known risk of anthracycline treatment.Anthracycline induced cardiotoxicity may be manifested by early or late events. Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and / or electrocardiogram (ECG) abnormalities such as non specific ST T wave changes. Tachyarrhythmias, including premature ventricular contractions 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 considered an indication for the suspension of doxorubicin treatment.

Cardiotoxicity may occur at lower doses in patients with prior medistina /pericardial irradiation, concomitant use of other cardiotoxic drugs, doxorubicin exposure at an early age, and advanced age. Data also suggest that pre-existing heart disease is a co-factor for increased risk of doxorubicin cardiotoxicity. In such cases, cardiac toxicity may occur at doses lower than the recommenced cumulative dose of doxorubicin. Studies have suggested that concomitant administration of doxorubicin and calcium channel entry blockers may increase the risk of doxorubicin cardiotoxicity. The total dose doxorubicin administered to the individual patient should also take into account previous or concomitant therapy with related compounds such as daunorubicin, idarubicin and mitoxantrone. Although not formally tested, it is probable that the toxicity of doxorubicin and other anthracyclines or anthracenediones is addictive. Cardiomyopathy and / or congestive heart failure may be encountered several months or years after discontinuation of doxorubicin therapy.

Pregnancy Category D: Safe use of doxorubicin in pregnancy has not been established. Doxorubicin is embryotoxic and teratogenic in rats and embryotoxic and abortifacient in rabbits. There are no adequate and well - controlled studies in pregnant women. If doxorubicin is to be used during pregnancy, or if the patient become pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

DESCRIPTION

Each sterile vial of DOXORUBA™ contains red coloured solution containing Doxorubicin Hydrochloride. Doxorubicin Hydrochloride is an antiblastic anthracycline antibiotic from the culture of Streptomyces peucetius var. Caesius Chemically, Doxorubicin hydrochloride is 5,12-Naphthacenedione, 10 - [(3 amino - 2,3,6 - trideoxy - a - L - *lyxo* - hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11 trihydroxy - 8 - (hydroxylacetyl) -1 methoxyhydrochloride (8S - *cis*) -. The structural formula is as follows :



$C_{27}H_{29}NO_{11}HCl$ M.W.=579.99

COMPOSITION

DOXORUBA™ 10 mg/5 ml and 50 mg/25 ml filled in amber glass vial.

Each ml contains:

Doxorubicin Hydrochloride IP	2 mg
Sodium Chloride IP	9 mg
Hydrochloric Acid IP (To adjust pH)	q.s
Water for Injection IP	q.s

INDICATIONS & USAGE

Doxorubicin have been used successfully to produce regression in a variety of neoplastic conditions, such as carcinoma of the breast, lung, bladder, thyroid, and also ovarian carcinoma; bone and soft tissue sarcoma; Hodgkin's and non Hodgkin's lymphoma, neuroblastoma, wilms tumor, acute lymhoblastic leukemia and acute myeloblastic leukemia. Doxorubicin has given positive results in superficial bladder tumor when administered intravesically, both after transurethral resection (as prophylaxis) and for therapeutic reasons. Other solid tumors have also responded, but the study of these is at present too limited to justify specific indications.

CLINICAL PHARMACOLOGY

Mechanism of Action: The mechanism of action of Doxorubicin is related to the ability of the antibiotic to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration by the antibiotic & its main localization in the perinucleolar chromatin. Rapid inhibition of mitotic activity & nucleic acid synthesis have also been demonstrated together with the appearance of chromosomal aberrations.

Pharmacokinetics: Pharmacokinetic studies have shown that intravenous administration of Doxorubicin is followed by a rapid fall in plasma levels, accompained, however, by slow urinary and biliary excretion. This is probably due to binding of the antibiotic to tissues. Urinary excretion as determined by fluorimetric methods, accounts for approximately 5% of the administered dose in 5 days; biliary excretion is the major elimination route, with 40% - 50% of the administered dose recovered in the bile of faeces in seven days. Impaired liver function causes slower excretion of the drug and in consequence, increased accumulation in plasma and tissues. Doxorubicin does not cross the blood brain barrier.

CONTRAINDICATIONS

Therapy of Doxorubicin is contraindicated in patients with active myelosuppression induced by previous chemo antiblastic or by radio therapy, and in patients already treated with the recommended cumulative dose of Doxorubicin.Doxorubicin is not recommended in patients with cardiopathy, or with a record of cardiopathy, although conclusive data are not yet available on the importance of this risk factor concerning Doxorubicin induced cardiac toxicity. Topical intravesical therapy with Doxorubicin is also contraindicated in patients with bladder tumors complicated by narrowing of the urethra which prevents the use of urethral catheters, or by urinary tract infections resistant to usual therapy. Hypersensitivity to hydroxybenzoates is a contraindication.

PRECAUTIONS

General: Doxorubicin is not an anti-microbial agent. Doxorubicin is emetogenic Antiemetics may reduce nausea and vomiting; prophylactic use of antiemetics should be considered before administration of doxorubicin; particularly when given in conjuction with other emetogenic drugs.

Nursing Mothers: Doxorubicin and its major metabolite, doxorubicinol, have been detected in the milk of atleast one lactating patient. Because of the potential for serious adverse reactions in nursing infants from doxorubicin, mothers should be advised to discontinue nursing during doxorubicin therapy.

Geriatric use: An estimated 4600 patients who were 65 and over included in the reported clinical experience of doxorubicin use for various indications.

No overall differences in safety and effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. The decision to use doxorubicin in the treatment of older patients should be based upon a consideration of overall performance status and concurrent illness, in addition to age of the individual therapy.

Pediatric use: Pediatric patients are at increased risk for developing delayedcardiotoxicity. Follow up cardiac evaluations are recommended periodically to monitor for this delayed cardiotoxicity.

Carcinogenesis, mutagenesis and impairment of fertility: Formal long-term carcinogenicity studies have not been conducted with doxorubicin. Doxorubicin and related compounds have been shown to have mutagenic and carcinogenicproperties when tested in experimental models (including bacterial systems,mammalian cells in culture, and female Sprague Dawley rats). The possible adverse effect on fertility in males and females in humans or experimental animals have not been adequately evaluated. Testicular atrophy was observed in rats and dogs.

ADVERSE REACTIONS

Intravenous route: Myelosuppression and cardiotoxicity are the two major adverse reactions. Alopecia is the most frequent adverse reaction and occur in about 85 % of cases treated. In males, it is accompanied by an arrest of beard growth. It is usually reversible at the end of treatment; stomatitis may occur about 5 - 10 days after administration: it is characterized by painful eroded areas particularly along the sides of the tongue and on the sublingual mucosa. Dosage regimens in which DOXORUBA™ is given on three consecutive days cause a greater incidence and severity of stomatitis. Gastrointestinal disorders, such as nausea, vomiting and diarrhea may also occur. Several tissue lesions, including necrosis, will occur. During administration of DOXORUBA™, if there is extravasation especially in the case of small veins used for repeated administrations, venous sclerosis has been reported.

Intravesical route: The following adverse reactions can occur; hematuria, vesical and urethral burning or stringing, dysuria, stangury and frequency of micturition. These reactions are usually of moderate intensity and are of short duration.

DOSAGE & ADMINISTRATION

Care in the administration of DOXORUBA™ will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of DOXORUBA™, extravasation may occur with or with out an accompanying burning or stinging sensation, even if blood returns well an aspiration of the infusion needle. If any signs or symptoms or extravasation have occured, the injection or infusion should be immediately terminated and restarted in other vein. If extravasation is suspected, intermittent application of ice to the site for 15 min. q.i.d. x 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature extravasation reaction, close observation and plastic surgery consultation is recommended. Blistering, ulceration and / or persistent pain are indications for wide excision surgery, followed by split thickness skin grafting.

The most commonly used dose schedule when used as single agent is 60 to 75 mg/m^2 as a single intravenous injection administered at 21 - day intervals. The lower dosage should be given to patients with indaquate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration.

DOXORUBA™ has been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic diseases, combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated. When used in combination with other chemotherapy drugs, the most commonly used dosage of DOXORUBA™ is 40 to 60 mg/m^2 given as singleintravenous injection every 21 to 28 days.

In a large randomized study (NSABP B 15) of patients with early breast cancer involving axillary lymph nodes, the combinations dosage regimen of AC was administered intravenously on day 1 of each 21 - day treatment cycle, four cycles of treatment was established.

Reconstitution Directions: It is recommended that DOXORUBA™ be slowlyadministrated into the tubing of a freely running intravenous infusion of sodium chloride injection or 5 % dextrose injection. The tubing should be attached to a butterfly needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of vein and the dosage. However, the dose should be administered in not less than 3 to 5 min. Local erythematous streaking along the vein as well as facial flushing may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

DOXORUBA™ should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that precipitate may form. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin. Until specific compatibility data are available, it is not recommended that DOXORUBA™ be mixed with other drugs. Parenteral drugs products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

DRUG INTERACTIONS

DOXORUBA™ is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect Doxorubicin