oncogen

Doxetran

(Doxorubicin)

ڈوکسیٹران

(ڈوکسو روبیسن)

WARNING: CARDIOMYOPATHY, SECONDARY MALIGNANCIES, EXTRAVASATION AND TISSUE NECROSIS, AND SEVERE MYELOSUPPRESSION

Cardiomyopathy: Myocardial damage can occur with doxorubicin hydrochloride with incidences from 1% - 20% for cumulative doses from 300mg/m² to 500mg/m² when doxorubicin hydrochloride is administered every 3 weeks. The risk of cardiomyopathy is further increased with concomitant cardiotoxic therapy. Assess left ventricular ejection fraction (LVEF) before and regularly during and after treatment with doxorubicin hydrochloride.
Secondary Malignancies: Secondary acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) occur at a higher incidence in patients treated with anthracyclines, including doxorubicin hydrochloride.
Extravasation and Tissue Necrosis: Extravasation of doxorubicin hydrochloride can result in severe local tissue injury and necrosis requiring wide excision and skin grafting. Immediately terminate the drug, and apply ice to the affected area.
Severe myelosuppression resulting in serious infection, septic shock, requirement for transfusions, hospitalization, and death may occur.

1. NAME OF THE MEDICINAL PRODUCT

Doxetran Injection 10mg/5ml
Doxetran Injection 50mg/25ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxetran Injection 10mg/5ml: Each 5ml contains doxorubicin hydrochloride.....10 mg
Doxetran injection 50mg/25ml: Each 25ml contains doxorubicin hydrochloride..... 50mg

3. PHARMACEUTICAL FORM

A translucent red coloured solution. Solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Acute leukemia
- Wilms tumor
- 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.

The main antitumor activities are listed in Table 1

Table 1: Doxorubicin Hydrochloride main anti-tumor activities.

Tumor Type	Response Rate (%)	Median Duration (month)	First Line Chemotherapy
Established Activity			
Breast	35	3-6	√
Ovary	38	3-6	?
Lung	30	3	?
Sarcoma	30	4	√
Wilms'	66	4	√
Bladder	28	4-6	√
Neuroblastoma	41	4	√
Hodgkin's	40	4-6	√
Non-Hodgkin's Lymphoma	40	4-6	√
Acute Leukemia	35	3	√
Hepatoma	32	4-6	√
Thyroid	30	6-10	√
Some Response			
Stomach	30	2-4	√?
Cervix	32	2-6	?
Head & Neck	19	2-4	
Testicle	20	3-6	
Myeloma	33	3	
Endometrial	36	4-6	
Unresponsive			
Colorectal			
Pancreas			
Renal			
Melanoma			
Brain			

4.2. Dose and method of administration

Dosage: The usual recommended dose is 60–75mg/m², given as a single intravenous injection every 21 days. A lower dose is advised for patients who have weakened bone marrow due to older age, previous treatments, or cancer involving the bone marrow. An alternative dosing schedule is 30mg/m² given once daily for three consecutive days, and this cycle is repeated every 4 weeks. The adult dosing regimen may also be used for children, when appropriate. The total lifetime cumulative dose of doxorubicin should not exceed 550mg/m² of body surface area. Doxorubicin has been administered as an intra-arterial infusion for 1-3 days at doses of 45-100mg/m². It is recommended that the total cumulative dose of doxorubicin for adults aged 70 or older be restricted to 450mg/m² body surface area.

Method of Administration:

Protective measures: Because doxorubicin is a cytotoxic (toxic) medicine, the following precautions should always be taken when preparing or handling it:

- Only trained personnel should prepare and handle the drug, using proper techniques.
- Pregnant staff must not handle or prepare this medication.
- Wear protective equipment at all times: including goggles, disposable gloves, gowns, and face masks.
- Reconstitution should be done in a designated area, ideally under a laminar airflow hood. Cover the work surface with disposable, absorbent, plastic-backed paper.
- All materials used during preparation, administration, or cleaning (including gloves) should be disposed of in high-risk waste bags and sent for high-temperature incineration.
- If any spillage or leakage occurs, clean it immediately using a 1% sodium hypochlorite (bleach) solution, preferably by soaking, and then rinse the area well with water.
- All cleaning materials used for decontamination should be discarded as hazardous waste.
- If skin contact occurs, wash the affected area thoroughly with soap and water or sodium bicarbonate solution. Avoid scrubbing or irritating the skin.
- If eye contact occurs, hold the eyelid(s) open and flush the eye(s) with plenty of clean water for at least 15 minutes, then seek medical attention immediately.
- After completing the procedure, always wash hands carefully after removing gloves.

Intravenous Infusion:

- Doxorubicin should be given slowly into the tubing of a freely running IV infusion of either 0.9% sodium chloride or 5% dextrose solution. Use a butterfly needle placed in a large vein whenever possible.
- The infusion should take at least 3–5 minutes. Direct IV push is not advised because of the risk of extravasation (leakage into surrounding tissue), which can occur even if blood return appears normal.
- If redness along the vein or facial flushing occurs, it may indicate that the infusion is too rapid. A burning or stinging sensation suggests leakage outside the vein, stop the infusion immediately and restart in another vein.

Intravesical Administration

- For intravesical use, the bladder should first be emptied using a catheter. Dilute doxorubicin to a final concentration of 80mg in 100mL of normal saline and instill the solution into the bladder through the catheter.
- After instillation, remove the catheter and instruct the patient to change position every 15 minutes (side to side) for one hour to ensure full contact of the drug with the bladder wall. The patient should avoid urination for one hour, after which the bladder may be emptied. This procedure is usually repeated monthly.
- Doxorubicin should not be mixed with other drugs or alkaline solutions, as this can cause degradation or precipitation. It is incompatible with heparin and fluorouracil, if these agents are used concurrently, flush the IV line thoroughly between infusions to avoid interaction.

Dosage adjustments:

Use in hepatic impairment: Doxorubicin dosage must be reduced if hepatic function is impaired according to the following table 2:

Table 2: Recommended dose for patients with hepatic impairment

Serum Bilirubin Levels	BSP Retention	Recommended Dose
20- 50 µmol/L	9 – 15 %	½ normal dose
>50 µmol/L	>15%	¼ normal dose

Use in the Elderly: Elderly patients may have reduced bone marrow reserves; therefore, a lower starting dose should be considered. For adults aged 70 years or older, the maximum cumulative lifetime dose of doxorubicin should be limited to 450mg/m² of body surface area to minimize the risk of heart toxicity.

Other Special Populations: Dose reduction or extended dosing intervals may be required for previously treated patients, obese individuals, or those with bone marrow involvement by cancer.

4.3. Contraindications:

Doxorubicin should not be used in patients who:

- Are allergic to doxorubicin, any of its ingredients, or similar medicines (such as other anthracyclines or anthracenediones).
- Are pregnant or breastfeeding (see Section 4.6 for details).

For Intravenous (IV) Administration: Doxorubicin must not be given if the patient has:

- Ongoing or severe bone marrow suppression or severe mouth ulcers caused by previous chemotherapy or radiotherapy.
- Active or widespread infections.
- Serious heart rhythm problems or heart failure.
- A recent heart attack.
- Severe liver problems.
- Already received the maximum allowed dose of doxorubicin or similar medicines (such as daunorubicin, epirubicin, idarubicin, or other anthracyclines).

For Intravesical (Bladder) Administration: Doxorubicin should not be used if the patient has:

- Tumors that have invaded the bladder wall.
- Urinary tract infections or bladder inflammation.
- Difficulty in catheterization (for example, due to large bladder tumors).
- Blood present in the urine (hematuria).

4.4. Warning

General: Doxorubicin is intended for intravenous or intravesical use only and must never be administered intramuscularly or subcutaneously, as severe local tissue necrosis can occur if there is extravasation. Treatment should be carried out only by physicians experienced in cytotoxic chemotherapy. Before starting therapy, patients must recover from any acute toxic effects of prior chemotherapy (such as mucositis, low blood counts, or infections). Baseline assessments should include complete blood counts, liver function tests (bilirubin, AST), renal function (creatinine), and cardiac evaluation by measuring left ventricular ejection fraction (LVEF). Myelosuppression is common and may be severe, requiring close monitoring and supportive care for neutropenia or infection. Cardiotoxicity is dose-related and may lead to irreversible heart failure, particularly at cumulative doses approaching 550mg/m², or at lower doses in patients with previous mediastinal radiation or concurrent cyclophosphamide use. Regular cardiac monitoring is essential throughout therapy. Dose reduction is recommended in patients with impaired liver function, and caution should be used when doxorubicin is administered with other potentially cardiotoxic or myelosuppressive drugs.

Cardiac Functions:

Cardiotoxicity is a known and serious risk associated with anthracycline therapy, including doxorubicin. It may occur early (acute) during treatment or late (delayed) months or even years after completion of therapy.
Early (Acute) Effects: Early cardiac effects are usually transient and may include sinus tachycardia, ECG changes (such as non-specific ST-T wave abnormalities), or occasional arrhythmias including premature ventricular contractions, ventricular tachycardia, bradycardia, atrioventricular block, or bundle-branch block. These changes are generally not predictive of delayed cardiotoxicity and rarely require discontinuation of treatment.
Delayed (Chronic) Effects: Delayed cardiotoxicity may appear late in the course of therapy or 2–3 months after treatment, and in some cases years later. It is characterized by reduced left ventricular ejection fraction (LVEF) and/or symptoms of congestive heart failure (CHF), including:

- Shortness of breath, tachycardia, pulmonary or peripheral edema.
- Cardiomegaly, hepatomegaly, pleural effusion, or ascites.

Subacute conditions such as pericarditis or myocarditis may also occur. Severe CHF is the most serious form of doxorubicin-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of this drug.
Dose Relationship and Risk: The likelihood of developing doxorubicin-related heart failure increases with the total cumulative dose: 1–2% at 300mg/m², 3–5% at 400mg/m², 5–8% at 450mg/m² and 6–20% at 500mg/m².
The risk rises sharply at doses above 450–550mg/m². Cardiotoxicity may also occur at lower doses in patients with pre-existing cardiac disease, prior mediastinal or pericardial irradiation, or concurrent cardiotoxic therapies such as cyclophosphamide, trastuzumab, or calcium-channel blockers. For such patients, the maximum cumulative dose should not exceed 450mg/m².
Pediatric Considerations: Children are more vulnerable to delayed cardiac toxicity, which can impair heart growth and function, sometimes leading to heart failure later in life. Up to 40% of pediatric patients may develop subclinical cardiac dysfunction, and 5–10% may develop symptomatic heart failure during long-term follow-up.
Monitoring and Prevention: Baseline and periodic evaluation of cardiac function is essential for all patients receiving doxorubicin. Recommended assessments include: Electrocardiogram (ECG) and Echocardiography (ECHO) or Multigated Radionuclide Angiography (MUGA) to measure LVEF.
A decrease in LVEF by ≥10% from baseline to a value below 50%, or an absolute LVEF <45%, indicates deteriorating cardiac function and requires reevaluation of therapy. Patients at higher risk (elderly, prior anthracycline use, concurrent cardiotoxic drugs, or radiation exposure) should undergo more frequent cardiac monitoring.
Management: If cardiac dysfunction is detected, doxorubicin treatment should be stopped immediately. Management includes digitalis, diuretics, ACE inhibitors, and other standard treatments for heart failure. Although symptoms may improve with treatment, anthracycline-induced cardiomyopathy is often irreversible.

Additional Guidance

- Avoid anthracycline therapy within 7 months of trastuzumab administration due to its prolonged half-life and additive risk.
- Consider lower total doses or alternative regimens for patients with risk factors.
- The total dose of doxorubicin and related agents (daunorubicin, idarubicin, mitoxantrone) should be considered cumulatively, as their cardiotoxic effects are additive.

Hematologic Toxicity:

Doxorubicin, like other cytotoxic agents, can cause myelosuppression, which is the most common and significant dose-limiting toxicity of this medicine. Before and during each treatment cycle, complete blood counts (CBC): including differential white blood cell (WBC) counts, red blood cell (RBC) counts, and platelet counts, should be carefully monitored.
Leucopenia and neutropenia are the predominant effects and occur in nearly all patients receiving effective doses of doxorubicin. These effects are dose-dependent and reversible.

- The lowest white blood cell counts (nadir) typically occur 10 to 14 days after administration.
- Recovery usually occurs by day 21 of the treatment cycle.
- Thrombocytopenia and anemia may also develop, though less frequently.

Patients who have had prior radiotherapy, bone marrow infiltration by tumor, or impaired liver function (without appropriate dose adjustment) may experience more severe myelosuppression. Simultaneous administration with other myelosuppressive drugs can lead to additive toxicity and should be used with caution. Because doxorubicin is also a potent but temporary immunosuppressive agent, patients are at increased risk of infection. Preventive and supportive measures should be taken as necessary.

Clinical consequences of severe myelosuppression may include:

- Fever and infection
- Sepsis or septic shock
- Hemorrhage
- Tissue hypoxia
- In severe cases, death

If significant myelosuppression occurs, dose reduction, treatment delay, or temporary discontinuation of doxorubicin may be required.

Secondary Leukaemia:

Secondary leukaemia, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), has been reported in patients receiving anthracycline-based chemotherapy, including doxorubicin.
This risk is higher in patients who have:

- Received combination therapy with DNA-damaging antineoplastic agents (e.g., alkylating agents such as cyclophosphamide)
- Been treated with concurrent or prior radiotherapy
- Been heavily pre-treated with cytotoxic drugs
- Received escalated or high cumulative doses of anthracyclines

Cases of secondary leukemia have also been observed in adjuvant and neoadjuvant breast cancer settings. The latency period between treatment and onset of leukemia typically ranges from 1 to 3 years. Data from large studies, such as those conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), indicate that the overall incidence of therapy-related AML or MDS following doxorubicin-based regimens is rare, estimated at approximately 0.2–0.5% within 5 years, but may be higher in patients receiving high-dose cyclophosphamide, radiotherapy, or in those aged 50 years or older. Pediatric patients are also susceptible and may develop secondary AML after anthracycline therapy.
Because of this potential long-term risk, patients who have received doxorubicin should undergo periodic follow-up and hematological monitoring after treatment completion.

Gastrointestinal Toxicity:

Doxorubicin commonly causes gastrointestinal side effects, which may range from mild nausea to severe mucosal injury. Nausea and vomiting occur frequently and may be severe. These effects are generally dose-related and can usually be controlled with antiemetic therapy. Mucositis (stomatitis and esophagitis) is a frequent and painful complication of doxorubicin therapy. It typically appears 5–10 days after starting treatment and often resolves within another 5–10 days. Mucositis may begin as a burning or sore sensation in the mouth or throat and can progress to ulceration involving the oral cavity, pharynx, esophagus, rectum, or vagina, increasing the risk of secondary infections. The incidence and severity of mucositis are greater when doxorubicin is administered on three consecutive days or in patients who have received prior mucosal irradiation. Most patients recover by the third week of therapy. Severe gastrointestinal complications such as ulceration or necrosis of the colon (particularly the cecum) have been reported, sometimes leading to bleeding, infection, or fatal outcomes, especially in patients receiving doxorubicin with cytarabine for acute non-lymphocytic leukemia. Other reported effects include anorexia, abdominal pain, diarrhea, dehydration, and hyperpigmentation of the oral mucosa.

Effects at the Site of Injection and Extravasation:

Local Reactions: Administration of doxorubicin may cause phlebosclerosis (hardening or thickening of the vein), especially when the drug is injected into small veins or repeatedly into the same vein. Adhering to the recommended administration techniques can help reduce the risk of phlebitis or thrombophlebitis at the injection site.
Extravasation: Accidental leakage of doxorubicin outside the vein (extravasation) during intravenous administration can lead to pain, burning, or stinging sensations, followed by severe local tissue injury, including inflammation, blistering (vesication), cellulitis, or necrosis. Extravasation may occur even if blood return appears adequate during needle aspiration. If any signs or symptoms of extravasation are observed, the infusion must be stopped immediately, and the injection should be restarted in another vein. Prompt local management and medical evaluation are essential to prevent or minimize tissue damage.

Hepatic Impairment:
Doxorubicin is primarily eliminated through the liver and bile (hepatobiliary system). Therefore, impaired liver function can lead to slower drug clearance and a higher risk of toxicity. Before each dose, liver function tests, including AST (SGOT), ALT (SGPT), alkaline phosphatase, and total bilirubin, should be performed to assess hepatic function. These tests should also be repeated periodically during treatment. Patients with elevated serum bilirubin may require a dose reduction, as they are more likely to experience increased side effects due to slower elimination of the drug. Doxorubicin is contraindicated in patients with severe hepatic impairment (e.g., Child-Pugh Class C or serum bilirubin levels greater than 5mg/dL). Changes in liver function caused by other concurrent medications or disease conditions may alter doxorubicin's metabolism, therapeutic activity, or toxicity, and such patients should be closely monitored throughout therapy.

Tumor Lysis Syndrome:
As with other cytotoxic agents, treatment with doxorubicin may cause tumor lysis syndrome (TLS) due to the rapid destruction of cancer cells. This process can lead to elevated levels of uric acid, potassium, phosphate, and creatinine, and may result in kidney dysfunction or other metabolic complications. Patients should have their serum electrolytes, uric acid, and renal function monitored closely during treatment. Preventive measures such as adequate hydration, urine alkalinization, and allopurinol prophylaxis are recommended to reduce the risk and severity of tumor lysis syndrome.

Immunosuppression and Risk of Infection:
Doxorubicin is a potent immunosuppressive agent, and treatment can temporarily reduce the body's ability to fight infections. The risk of bacterial, viral, or fungal infections increases, particularly during periods of myelosuppression when white blood cell counts are low. Patients with active infections should not begin doxorubicin therapy until the infection is adequately treated. Those who develop infections during treatment should receive appropriate antimicrobial therapy and supportive care as required. Because of its immunosuppressive effect, live or live-attenuated vaccines should be avoided during treatment with doxorubicin and in patients with compromised immune function. If vaccination is necessary, inactivated vaccines may be considered, but the response could be less effective. Patients should be monitored closely for signs of infection, such as fever, sore throat, or chills, and should promptly report these symptoms to their healthcare provider.

Intravesical Route:
When doxorubicin is administered intravesically (directly into the bladder), it may cause symptoms of chemical cystitis, such as: Pain or burning during urination (dysuria), Increased frequency or urgency of urination (polyuria, nocturia, stranguria), Blood in urine (hematuria), Bladder discomfort or pain and In severe cases, inflammation, necrosis, or bladder wall constriction. Care should be taken during catheterisation, particularly in patients with large bladder tumors that may obstruct the urethra. During intravesical therapy, urine cytology and blood counts should be monitored monthly, and cystoscopic examinations should be performed periodically to assess bladder condition and treatment response.

Instructions to be Given to Patients:

- Injection Site: Patients should immediately inform their doctor or nurse if they feel pain, burning, or stinging at the injection site during or after administration.
- Nausea and Vomiting: Nausea and vomiting may occur 3–6 hours after treatment and can last for several hours. Your doctor may prescribe anti-nausea medication to help relieve these symptoms.
- Urine Colour: It is normal for urine to appear reddish for 1–2 days after receiving doxorubicin. This is due to the colour of the drug and is not a sign of bleeding.
- Hair Loss: Hair loss (alopecia) may begin 1–2 weeks after starting treatment. Hair loss may be temporary or complete, but hair usually grows back after therapy is finished. (In some settings, scalp cooling or protective methods may help reduce hair loss.)
- Appetite: Loss of appetite (anorexia) may occur for about 24 hours after treatment and may occasionally last a few days.
- Skin and Nail Changes: Darkening of the skin, nails, or inside of the mouth (hyperpigmentation) may occur during treatment. This change is generally harmless and may persist after therapy.
- Fertility: Doxorubicin can temporarily or permanently affect fertility in both men and women.
  - o Women may stop having menstrual periods (amenorrhoea) during treatment, but normal cycles often return within a few months after therapy, along with normal fertility.
  - o Men may experience a decrease or loss of sperm (oligospermia or azoospermia), which can sometimes be permanent. In some cases, fertility may return years after treatment.
  - o Male patients are advised to use effective contraception during and after therapy to prevent pregnancy.
- Medical History: Patients should inform their doctor about any heart or liver conditions before starting doxorubicin, as these may affect the dose and treatment plan.

Use in Special Populations:

- **Elderly Patients:** Elderly patients may have reduced bone marrow reserves and are therefore at greater risk of myelosuppression and other toxicities. A lower dose of doxorubicin may be required in such patients. It is generally recommended that the total cumulative lifetime dose of doxorubicin for adults aged 70 years or older should not exceed 450mg/m² of body surface area. Clinical studies have not shown major differences in overall safety or effectiveness between elderly and younger adults, but careful monitoring of cardiac and hepatic function is advised.
- **Paediatric Patients:** Children and adolescents are more susceptible to delayed cardiotoxicity after treatment with doxorubicin, and females may be at a slightly higher risk. Long-term cardiac follow-up is recommended for all paediatric patients who have received doxorubicin. In addition, use in children may affect growth or temporary gonadal function, especially when given as part of intensive chemotherapy regimens.
- **Embryo-Fetal Toxicity and Contraception:** Doxorubicin is genotoxic and may cause harm to the developing fetus if administered during pregnancy. Both male and female patients should use effective contraception during treatment and for a period after therapy. Patients who wish to have children after treatment should consider genetic counselling where available.

4.5. Interactions with Other Medicines and Treatments

Doxorubicin and Enzymes (CYP3A4, CYP2D6, P-gp): Doxorubicin is processed in the body by certain enzymes (CYP3A4, CYP2D6) and a transport protein (P-glycoprotein). Medicines that block these enzymes or proteins (e.g., verapamil) can increase the levels of doxorubicin in the blood, which may raise the risk of side effects. On the other hand, medicines or substances that speed up these enzymes or proteins (e.g., phenobarbital, phenytoin, St. John's Wort) may reduce doxorubicin levels, potentially making it less effective.

Combination with Other Chemotherapy Drugs: Doxorubicin is often used with other cancer treatments. When combined, the risk of side side effects, especially those affecting the bone marrow, blood cells, and digestive system, may increase.

Adjuvant Chemotherapy: Doxorubicin is not routinely recommended as part of adjuvant (supportive) chemotherapy for all cancers. Its effectiveness and safety depend on the drugs it's used with and how they are given. If doxorubicin is to be used in this way, approval from hospital specialists or the ethics committee is advised.

Specific Drug Interactions:

- **Cyclophosphamide:** Increases the risk of heart damage when used with doxorubicin. Doxorubicin may also worsen bladder irritation caused by cyclophosphamide.
- **Ciclosporin:** May increase doxorubicin levels and lead to more severe and longer-lasting effects on the blood. Seizures and coma have been reported when both drugs are used together.
- **Heparin:** Should not be mixed with doxorubicin in the same solution, as they may form a solid (precipitate).
- **Radiotherapy (including Mediastinal Radiotherapy):** Using radiotherapy with doxorubicin may increase the risk of heart problems, skin reactions, and mouth/throat inflammation (mucositis).
- **Paclitaxel:** Giving paclitaxel before doxorubicin may slightly increase doxorubicin levels. This effect is smaller if doxorubicin is given first.
- **Propranolol:** Both drugs may affect heart function by interfering with energy production in heart cells, potentially increasing the risk of heart-related side effects.
- **Sorafenib:** May slightly increase doxorubicin levels in the body, although the importance of this effect is not yet clear.

4.6. Fertility, Pregnancy, and Breastfeeding

Effects on Fertility: Doxorubicin may affect fertility in both men and women during treatment. In women, it can cause periods to stop (amenorrhea). Periods may return after treatment, but early menopause is possible. In men, doxorubicin may reduce sperm production or cause infertility. These effects may be long-term or permanent, although sperm levels can recover in some cases, sometimes years after treatment ends. Doxorubicin can damage sperm DNA. Men should use reliable contraception during treatment and for at least 3 months and 10 days after the last dose. Both men and women are advised to discuss fertility preservation options (such as sperm or egg storage) with their doctor before starting treatment.

Pregnancy (Category D): Doxorubicin should not be used during pregnancy unless it is clearly necessary and the potential benefits outweigh the risks. If a woman is pregnant or becomes pregnant during treatment, she should be informed about the possible risks to the unborn baby. Although animal studies have not shown birth defects, they have demonstrated harmful effects on the developing embryo, including reduced fetal weight and pregnancy loss. Because doxorubicin can cause changes in chromosomes (genetic material), its use during pregnancy is generally not recommended.

Contraception Advice: Women of childbearing age should avoid becoming pregnant during treatment and must use effective contraception during treatment and for at least 6 months and 10 days after the last dose. Men with female partners who could become pregnant should also use effective contraception during treatment and for at least 3 months and 10 days after the last dose.

Breastfeeding: Doxorubicin can pass into breast milk and may harm a nursing infant. Breastfeeding is not recommended during treatment with doxorubicin and for at least 10 days after the final dose.

4.7. Adverse Effects (Undesirable Effects)

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

Table 3: Adverse Reactions Table

System Organ Class	Frequency	Adverse Reactions
Blood and Lymphatic System Disorders	Very common	Leucopenia, neutropenia, anemia, 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, diarrhea, vomiting, nausea
	Common	Esophagitis, abdominal pain
	Not known	Gastrointestinal hemorrhage, erosive gastritis, colitis, mucosal discoloration, large intestinal hemorrhage[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 ECG, abnormal transaminases, increased weight[b]
Metabolism and Nutrition Disorders	Very common	Decreased appetite
	Not known	Dehydration, hyperuricemia
Neoplasms Benign, Malignant and Unspecified	Not known	Acute lymphocytic leukemia, acute myeloid leukemia
Nervous System Disorders	Not known	Somnolence
Renal and Urinary Disorders	Not known	Chromaturia[c], renal disorder
Reproductive System and Breast Disorders	Not known	Amenorrhea, azoospermia, oligospermia
Skin and Subcutaneous Tissue Disorders	Very common	Palmar-plantar erythrodysesthesia 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, hemorrhage, thrombophlebitis, phlebitis, phlebosclerosis, hot flush, flushing

Footnotes:
a Reported in patients with acute myelogenous leukaemia treated with doxorubicin and cytarabine
b Reported in patients with early breast cancer receiving doxorubicin-containing adjuvant therapy (NSABP -15 trial)
c For one to two days after administration

4.8: Overdose

Acute overdose with doxorubicin may lead to serious toxicity, including: **Cardiac toxicity**, such as acute myocardial changes; **Severe myelosuppression**, primarily manifesting as leucopenia and thrombocytopenia; **Gastrointestinal toxicity**, particularly mucositis. **Delayed onset congestive heart failure** has been reported and may occur up to six months following overdose. Patients should be closely monitored, and any signs of cardiac dysfunction should be managed with standard treatment protocols. Fatal outcomes have occurred following single doses of 250mg or 500mg of doxorubicin. These doses may cause **acute myocardial damage** within 24 hours and **profound myelosuppression**, typically peaking between days 10 and 15 post-administration. No specific plasma concentration associated with toxicity has been defined. Doxorubicin is extensively bound to plasma proteins. While **hemoperfusion** initiated within minutes of overdose may reduce serum concentrations, **haemodialysis** is not expected to be effective. There is currently **no specific antidote** for doxorubicin overdose. Management should be supportive and symptomatic, with particular attention to maintaining **cardiac and respiratory function**. Continuous **cardiac monitoring** is advised. Special care should be taken to prevent and manage **infections and bleeding** that may result from prolonged bone marrow suppression.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action: Doxorubicin is an anti-cancer (cytotoxic) medicine that works by binding to DNA and blocking the production of nucleic acids (DNA and RNA), which are essential for cell growth and division. Although the exact way it works is not fully understood, laboratory studies have shown that doxorubicin: Enters cells quickly and binds to genetic material; Stops cells from dividing; Interferes with the production of DNA and RNA; Can cause mutations and changes in chromosomes. Doxorubicin also has immunosuppressive effects, meaning it can temporarily weaken the immune system. It has been shown to reduce antibody production in animal studies, and similar effects have been seen in humans. Doxorubicin is not specific to any one phase of the cell cycle, meaning it can affect cancer cells at various stages of their growth. Its toxic effects on bone marrow are thought to be due to its action on actively dividing myeloid (blood-forming) cells. The cardiotoxic effects (damage to the heart) appear to occur through different mechanisms. While it can reduce DNA production in heart cells in animal studies, this does not seem to fully explain the heart damage. Some evidence suggests that the generation of harmful free radicals may play a role in damaging heart tissue. There is experimental data showing that antioxidants, such as vitamin E and other free radical scavengers, may protect the heart from damage in animals without reducing the cancer-fighting effects of doxorubicin. However, these findings need to be confirmed in humans.

5.2 Pharmacokinetic Properties

Absorption and Distribution: Doxorubicin is not suitable for oral administration, as less than 5% of the drug is absorbed through the gastrointestinal tract. After intravenous administration, doxorubicin is rapidly cleared from the blood and distributes extensively into body tissues. It shows high tissue binding, but detailed data on plasma protein binding is not available. Doxorubicin does not cross the blood-brain barrier.

Metabolism: Doxorubicin is mainly metabolized in the liver, where it is converted into several compounds, including adriamycinol and other aglycone metabolites. Some of these breakdown products are also cytotoxic, but it is not clear whether they are more or less toxic than the original drug. Metabolism may be slower in patients with impaired liver function, which may increase drug levels in the body. Doxorubicin and its metabolites follow a three-phase elimination pattern from the plasma: First phase half-life: approximately 12 minutes, Second phase half-life: approximately 3.3 hours and Third phase half-life: approximately 29.6 hours

Excretion: Doxorubicin is primarily eliminated through the biliary system (via bile and faeces), which accounts for about 40%–50% of the administered dose within seven days. Only 4%–5% of the dose is excreted through the urine within five days. In patients with liver dysfunction, excretion is slower, which may lead to increased drug accumulation in the blood and tissues.

6. PHARMACEUTICAL PARTICULARS

6.1 Pack Sizes
For 10mg/5ml and 50mg/25ml
Single Vial is packed in unit carton with leaflet.

6.2 Storage Conditions
Store between 2-8°C. Don't Freeze.
Protect from light.

6.3 Instructions
To be sold on the prescription of registered medical practitioner only.
Keep out of reach of children.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: دوا کو ۲ سے ۸ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں
روشنی سے بچائیں۔ منجمد نہ کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔

For adverse event reporting, kindly email us at
pharmacovigilance@oncogenpharma.com.pk

7. MANUFACTURER

oncogen

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