

DBL DOXORUBICIN HYDROCHLORIDE

Name of medicine

Doxorubicin hydrochloride

Presentation

Doxorubicin hydrochloride Injection is supplied in solution form containing sodium chloride.

Doxorubicin hydrochloride for Injection is supplied as a freeze dried product containing Lactose as an excipient.

Uses

Actions

Although it is known that anthracyclines are able to interfere with a number of biochemical and biological functions within eukaryotic cells, the precise mechanisms of doxorubicin cytotoxic and/or antiproliferative properties have not been completely elucidated. The drug, once penetrated into a cell, mostly binds to chromatin. Experimental evidence indicates that doxorubicin forms a complex with the DNA by intercalation of its planar rings between nucleotide base pairs. The consequences of this intercalation are serious disturbances of DNA synthesis, DNA-dependent RNA synthesis and protein synthesis. However, the doxorubicin concentrations required to exert antiproliferative effects through these mechanisms appear somewhat greater than those achievable at the tumour site in the clinical setting. More recent experimental evidence seems to indicate that DNA intercalation triggers DNA cleavage by topoisomerase-II, yielding serious disturbances in the tertiary structure of DNA. This effect is seen with drug concentrations which have been found within the clinically therapeutic range. Doxorubicin is also known to be involved in oxidation/reduction reactions: a number of NADPH-dependent cellular reductases are able to reduce doxorubicin to semiquinone free radicals, which can in turn react with molecular oxygen to generate highly reactive cytotoxic compounds such as superoxide, hydroxyl radicals and hydrogen peroxide. Free radical formation has been implicated in doxorubicin cardiotoxicity. A further site of action for doxorubicin may be at the cell membrane level: the drug can bind to cell membrane lipids and affect a variety of functions. Cytotoxicity and/or antiproliferative activity of doxorubicin may result as a consequence of any mentioned mechanisms and there may be others.

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

Pharmacokinetics

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

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

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

Excretion: Following IV administration, plasma levels of doxorubicin follow a multiphasic decline, with a terminal half-life reported in the 20 to 48 hour range. The terminal half-life of 13-OH-doxorubicinol is similar to that of doxorubicin. Plasma clearance is in the range of 8 to 20 ml/min/kg, and is mainly due to metabolism and biliary excretion. This slow elimination from plasma might be further prolonged in patients

with impaired liver function. The clearance of doxorubicin occurs to a substantial extent by metabolic conversion to a number of less active or inactive products. Forty to fifty percent of the administered dosage is recovered in the bile or in the faeces in seven days. Renal excretion is modest, accounting for only 5% to 10% of the administered dose in 5 days.

Indications

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

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

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

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

Dosage and administration

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

Intravenous (IV) Administration:

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

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

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

Administration of doxorubicin in a weekly regimen has been shown to be as effective as the tri-weekly schedule. The recommended weekly dosage is 10-20mg/m²; this schedule of administration might be accompanied by reduced toxicity, particularly on the heart.

If doxorubicin is used in combination with other antitumour agents with potentially overlapping toxicities, the recommended dose per cycle is in the 30-60mg/m² range.

As doxorubicin is a myelosuppressive agent, the interval between cycles may need to be increased, or the drug dosage reduced, in patients whose WBC counts (particularly neutrophils) are below the range of normal values before any treatment cycle. Dosage may also need to be reduced in children, in the elderly, and in pre-treated patients in whom the marrow reserve might be low.

In the presence of impaired hepatic function it is suggested to reduce doxorubicin dosage (see Warnings and Precautions).

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

Intravesical Administration:

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

Intra-arterial Administration:

Doxorubicin has been also used by the intra-arterial route in an attempt to produce intense local activity with reduced general toxicity. Since this technique is potentially hazardous and can lead to widespread necrosis of the perfused tissue, intra-arterial administration should only be attempted by those physicians fully trained with this technique.

Intravenous administration

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

Preparation of Doxorubicin Hydrochloride for Injection

The contents of the vial for Doxorubicin Hydrochloride for Injection should be reconstituted with Water for Injection, Sodium Chloride 0.9% or Dextrose 5% injection to a solution concentration of 2 mg per mL.

The reconstituted solution is stable at room temperature, in the vial or in a polypropylene (Terumo) syringe, in the presence or absence of light for a period of 48 hours. However, it is recommended that the solution be stored at 2 to 8°C in a refrigerator, and used within 24 hours, in line with good pharmaceutical practice.

Contraindications

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

- persisting myelosuppression or severe stomatitis from previous cytotoxic treatments;
- presence of generalized infections;
- marked liver function impairment;

- severe arrhythmias, myocardial insufficiency, previous myocardial infarction;
- previous treatment with anthracyclines up to their maximum cumulative dose;
- hypersensitivity to doxorubicin or to other anthracyclines; or anthracenediones

Contraindications for intravesical use are:

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

Warnings and precautions

Treatment with doxorubicin should be carried out only by physicians experienced in cancer treatment and must be conducted under strict supervision, with a number of body functions being carefully monitored. Doxorubicin is not a microbial agent.

- *Complete blood cell counts:* These have to be performed with particular attention to total and differential WBC counts. Doxorubicin-induced bone marrow depression, primarily of leucocytes, requires careful haematologic monitoring since persistent severe myelo-suppression may result in superinfections or haemorrhages. At the doses/ schedules recommended for the treatment of solid tumours, a marked leucopenia may occur (WBC counts of $1000/\text{mm}^3$ or lower can be expected during treatment with full doses of doxorubicin), but such leucopenia is usually transient, reaching its nadir 10 to 14 days after treatment and with recovery usually completed by the 21st day. Platelet and erythrocyte levels should also be monitored. Haematologic toxicity may require dose reduction or suspension or delay of doxorubicin 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. Persistent severe myelosuppression may result in superinfection or haemorrhage.
- *Assessment of liver function:* Since doxorubicin is predominantly eliminated via the liver and bile, a delayed elimination of the drug can occur in the case of reduced liver function or difficult bile outflow and serious secondary effects can develop. Commonly used guidelines for dose reduction under conditions of impaired liver function in adult patients are based on serum bilirubin levels as follows:

Serum bilirubin levels	BSP retention	Recommended dose
20 to 50 micromoles/L	9 to 15 %	$\frac{1}{2}$ normal dose
Over 50 micromoles/L	Over 15 %	$\frac{1}{4}$ normal dose

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.

- *Cardiac Function:* Cardiotoxicity is a known risk of anthracycline treatment. The most severe and typical form of such toxicity is represented by a delayed cardiomyopathy which occurs with increased frequency with high cumulative doses of the drug and can result in congestive heart failure (CHF). Cardiac function should be assessed before undergoing treatment with doxorubicin and has to be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. Although endomyocardial biopsy is recognized as the most appropriate diagnostic tool to detect anthracycline-induced cardiomyopathy, this invasive examination may not be easily carried out on a routine basis.

The routine assessment of cardiac function during doxorubicin treatment may include electrocardiogram (ECG) and the evaluation of the left ventricular ejection fraction (LVEF). ECG changes are generally indicative of a transient toxicity, but a reduction of the QRS voltage, or a prolongation beyond normal limits of the systolic time interval may be indicative - as is a decrease of the LVEF - of typical anthracycline-induced cardiomyopathy. The probability of developing CHF, estimated around 1% to 2% at a cumulative dose of $300\text{mg}/\text{m}^2$, slowly increases up to the total cumulative dose of $450\text{--}550\text{mg}/\text{m}^2$; thereafter the risk of developing CHF increases steeply, and it is recommended not to exceed the total cumulative dose of $550\text{mg}/\text{m}^2$.

If any additional risk factor for cardiac toxicity is present, cardiac toxicity might occur at lower cumulative doses and the monitoring of cardiac function must be particularly strict. Risk factors for cardiac toxicity include a previous history of heart disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous treatments with anthracyclines or anthracenediones, concomitant use of other cardioactive compounds (e.g. calcium channel blocking drugs) or concomitant use of other potentially cardiotoxic drugs (e.g. cyclophosphamide, 5-fluorouracil or trastuzumab). Anthracyclines including doxorubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab, may also be at an increased risk of developing cardiotoxicity. The half-life of trastuzumab is approximately 28.5 days and may persist in the circulation for up to 24 weeks. Therefore, physicians should avoid anthracycline-based therapy for up to 24 weeks after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Doxorubicin induced cardiotoxicity mostly develops during the course of therapy up to two months from its termination but late events (several months to years after treatment termination) have occurred. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

- *Extravasation and rate of administration:* Extravasation of doxorubicin during IV injection may give rise to severe tissue lesions and necrosis. Venous sclerosis may result from injection into a small vessel or from repeated injections into the same vein. To minimize the risk of drug extravasation and make sure that the vein is properly flushed after drug administration, it is advisable to give the drug via the tubing of a freely running saline infusion after checking that the needle is properly placed in the vein.

The rate of administration is dependent on the size of the vein and the dosage. It is important that the dose be administered in not less than 3-4 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration.

Should signs of symptoms of extravasation occur during intravenous administration of doxorubicin, the drug infusion should be immediately terminated. To manage extravasation, the interventions approved by the physician and/or the health care institution must be immediately utilized.

- *Carcinogenicity, Mutagenicity and Impairment of Fertility:* Doxorubicin and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models.

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

Doxorubicin may cause infertility during the time of drug administration. In women, doxorubicin may cause amenorrhoea. 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 azospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing doxorubicin treatment should use effective contraceptive measures.

- *Tumour-Lysis Syndrome:* Like other cytotoxic drugs, doxorubicin may induce hyperuricaemia secondary to rapid lysis of neoplastic cells (tumour-lysis syndrome). The clinician should monitor the patient's blood uric acid level, potassium, calcium phosphate and creatinine, and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem.

Hydration, urine alkalinisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimise potential complications of tumour-lysis syndrome.

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

Concurrent use of doxorubicin with live virus vaccines may potentiate the replication of the vaccine virus, increase adverse effects of the vaccine, and /or may decrease the patient's antibody response to the vaccine. Doxorubicin may also decrease the patient's antibody response to killed virus vaccines. The interval between discontinuation of medications that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on many factors; estimates vary from three months to one year.

- It has been reported that doxorubicin may enhance the severity of the toxicity of anticancer therapies such as: cyclophosphamide induced haemorrhagic cystitis, mucositis induced by radiotherapy, and hepatotoxicity of 6-mercaptopurine. Radiation-induced toxicities (myocardium, mucosae, skin and liver) have also been reported.
- As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal), have been coincidentally reported with the use of doxorubicin.
- 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 full doses of the drug.
- Doxorubicin may impart a red colour to the urine. Patients should be advised that such an event should not be cause for alarm.

Pregnancy and Lactation

The safe use of doxorubicin in pregnancy has not been established. Doxorubicin is embryotoxic and teratogenic in rats; it is embryotoxic and may induce abortion in rabbits. Women of child-bearing potential who are to undergo doxorubicin therapy should be appraised of the potential hazard to the foetus and should be advised to avoid becoming pregnant during treatment. If doxorubicin has to be used during pregnancy, the potential benefits of the treatment must be carefully weighed against the possible risks to the foetus.

Given the mutagenic potential of doxorubicin, the drug could induce chromosomal damage in human spermatozoa; therefore, males undergoing doxorubicin treatment should employ contraceptive measures.

Doxorubicin is secreted into breast milk, therefore doxorubicin-treated women should be instructed not to breast-feed due to the potential for serious harm to nursing infants.

Effects on ability to drive and use machines

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

Other

Dental Work: Patients should not undergo dental work during treatment with Doxorubicin.

Adverse effects

- *Bone Marrow/Haematologic Toxicity:* A dose-dependent, reversible leucopenia and/or granulocytopenia (neutropenia) is the predominant manifestation of doxorubicin bone marrow/haematologic toxicity and represents the *acute* dose-limiting toxicity of this drug. During the most

commonly used 3-4 week administration schedule the nadir of leucocytes/granulocytes is generally reached 10 to 14 days following drug administration. In patients with normal bone marrow regenerative capacity, white blood cell counts usually recover by the end of the third week. If severe myelosuppression occurs, bone marrow support (e.g. peripheral blood progenitor cells and/or colony-stimulating factors) may be used. Thrombocytopenia and anaemia may also occur.

Clinical consequences of doxorubicin bone marrow/haematologic toxicity may be fever, infections, sepsis/septicemia, septic shock, haemorrhages, tissue hypoxia or death. Intravenous antibiotics should be given in the presence of febrile neutropenia. The occurrence of secondary acute myelogenous leukaemia, with or without a pre-leukaemic phase, has been reported rarely in patients concurrently treated with doxorubicin in combination with DNA-damaging antineoplastic agents. These leukaemias can have a short (1-3 years) latency period.

- **Cardiac Toxicity:** Anthracycline-induced cardiac toxicity may be manifested by early (or acute) or late (delayed) events. The early cardiac toxicity of doxorubicin mainly consists of sinus tachycardia and/or ECG abnormalities, e.g. non-specific ST-T wave changes, but tachyarrhythmias such as premature ventricular contractions, ventricular tachycardia, bradycardia as well as atrioventricular and bundle-branch block have also been reported. With the exception of malignant cardiac dysrhythmias, these effects are usually not predictive of subsequent development of delayed cardiotoxicity, are rarely of clinical importance and are generally not considered an indication for the suspension of doxorubicin treatment. The delayed cardiac toxicity is represented by a characteristic cardiomyopathy which clinically is manifested by symptoms/signs of ventricular dysfunction/CHF (such as dyspnoea, pulmonary oedema, dependent [e.g. ankle] oedema, hepato-megaly, ascites, pleural effusion, gallop rhythm). This toxicity appears to be dependent on the cumulative dose of doxorubicin and represents the cumulative dose-limiting toxicity of the drug. A number of studies have assessed that the risk of developing CHF increases steeply, in absence of other cardiac risk factors, after having reached a doxorubicin cumulative dose of 550mg/m²; however, if any additional risk factor for cardiac toxicity is present (e.g. active or dormant cardiovascular disease, previous mediastinal radiotherapy, previous/concomitant use of other cardiotoxic drugs) cardiac toxicity might occur at lower cumulative doses. Delayed cardiotoxicity mainly develops during the course of therapy with doxorubicin and up to two-three months afterwards, but late events (several months to years after treatment termination) have occurred. Serious cardiac impairment may be prevented through regular surveillance during the course of treatment (see also Warnings and Precautions). Subacute effects such as pericarditis/myocarditis have also been reported.
- **Gastrointestinal Toxicity:** Mucositis (mainly stomatitis, less often esophagitis) may occur in patients undergoing doxorubicin therapy. Clinical manifestations of mucositis include pain or burning sensation, erythema, erosions-ulcerations, bleeding, infections. Stomatitis generally appears early after drug administration and, if severe, may progress over a few days to mucosal ulcerations; however, most patients recover from this adverse event by the third week of therapy. Nausea, vomiting and, occasionally, diarrhoea and abdominal pain can also occur. Severe vomiting and diarrhoea may produce dehydration. Nausea and vomiting may be prevented or alleviated by the administration of appropriate antiemetic therapy. A combination of doxorubicin and cytarabine has given rise to bleeding, ulceration and necrosis of the colonic mucosa in patients with acute myelogenous leukaemia.
- **Cutaneous and Hypersensitivity Reactions:** Alopecia, including the interruption of beard growth, occurs frequently. This side effect is usually reversible, with regrowth of all hair occurring within two-three months from the termination of therapy. Flushes, skin and nail hyperpigmentation and hypersensitivity to irradiated skin ('radiation recall reaction') may also occur. Urticaria and anaphylaxis have been reported in doxorubicin-treated patients; signs/symptoms of these reactions may vary from skin rash and pruritus to fever, chills and shock. The 'hand-foot syndrome' ('palmar-plantar erythrodysesthesia', or 'acral erythema') has also been reported.
- **Effects at Site of Injection:** Erythematous streaking along the infused vein is not uncommon and may precede local phlebitis or thrombophlebitis. The risk of phlebitis/thrombophlebitis at the injection site may be minimised by following the procedure for administration recommended in Warnings and Precautions. Phlebosclerosis might also occur, particularly if doxorubicin is repeatedly infused into a small vein.
- In the case of perivenous drug extravasation, local pain, severe cellulitis and tissue necrosis will occur (see Warnings and Precautions).

- Other Adverse Reactions: Other adverse events include malaise/ asthenia, ocular toxicity (conjunctivitis, lacrimation) and hyperuricemia, which may occur as a consequence of the extensive purine catabolism which accompanies drug-induced rapid cell kill of highly chemosensitive neoplasms ('tumour lysis syndrome'); hydration, urine alkalinization and allopurinol administration will help to prevent or minimize the adverse effects of hyperuricemia.

Amenorrhoea may also occur and doxorubicin treatment may result in azoospermia in the seminal fluid.

Administration of doxorubicin by the intravesical route may give rise to chemical cystitis and bladder constriction.

Interactions

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

Doxorubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy and/or toxicity.

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.

Overdosage

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

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

Pharmaceutical precautions

Handling Precautions

As with all antineoplastic agents, trained personnel should prepare Doxorubicin. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling doxorubicin. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed, thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as doxorubicin.

Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

Items used to prepare Doxorubicin, or articles associated with body waste should be disposed of by placing in a double sealed polythene bag and incinerated at 1100°C.

Accidental contact with the skin or eyes should be treated immediately by copious lavage with water, or soap and water, or sodium bicarbonate solution; medical attention should be sought.

Spills and Disposal

If spill occurs, restrict access to the affected area. Wear two pairs of latex rubber gloves, a suitable mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as

absorbent towels or adsorbent granules. Spills may also be treated with 5% sodium hypochlorite. Collect the absorbent/adsorbent and other debris from the spill and place in a leakproof plastic container and label accordingly. Cytotoxic waste should be regarded as toxic and hazardous and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100°C'. Waste material should be incinerated at 1100°C for at least 1 second. Clean the remaining spill area with copious amounts of water.

Incompatibilities

Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin.

Doxorubicin should not be mixed with heparin or 5-fluorouracil since it has been reported that these drugs are chemically incompatible (formation of a precipitate). Doxorubicin should not be mixed with other cytotoxic drugs in the same vial or syringe during the administration of combination chemotherapy regimens.

Special Precautions for Storage

Store at 2 to 8°C (Refrigerate). Do not freeze. Protect from light.

Medicine classification

Prescription Medicine.

Package quantities

Doxorubicin Hydrochloride Injection is presented in vials containing doxorubicin as a sterile solution.

Strength	Pack Size
10 milligrams/5 mL vial	1
20 milligrams/10 mL vial	1
50 milligrams/25 mL vial	1

Doxorubicin Hydrochloride for Injection is presented in vials containing doxorubicin as a freeze dried product.

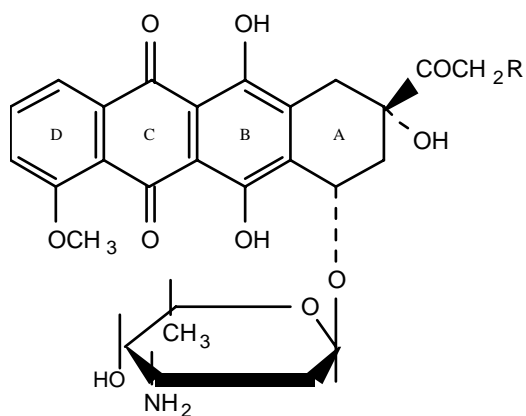
Strength	Pack Size
10 milligrams in ONCO-TAIN™ vial	1
20 milligrams in ONCO-TAIN™ vial	1

Further information

Preclinical Safety Data:

The LD₅₀ of doxorubicin was 21.9 and 12.5mg/kg for mice and rats, respectively, and about 2.0mg/kg for dogs. The main targets after a single drug dose were the haemolymphopoietic system and, especially in dogs, the gastrointestinal tract. The toxic effects after repeated administration were investigated in rats, rabbits and dogs. The main targets of doxorubicin in the abovementioned species were the haemolymphopoietic system, the gastro-intestinal tract, the kidneys, the liver and both male and female reproductive organs. Concerning the heart, acute, subacute and cardiotoxicity studies have indicated that doxorubicin was cardiotoxic in all the laboratory animals tested. Doxorubicin was genotoxic in most of the *in vitro* or *in vivo* mutagenicity tests performed, toxic to the reproductive organs, embryotoxic in rats and rabbits, and teratogenic in rats. There is no information available on the administration of doxorubicin in animals during the peri- and post-natal periods. Doxorubicin, like other anthracyclines and many cytotoxic drugs, was carcinogenic in rats. A local safety study in dogs has shown that extravasation of the drug causes tissue necrosis.

The chemical structure is shown below.



Doxorubicin R = OH

Daunorubicin R = H

Doxorubicin hydrochloride is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*. The chemical structure of doxorubicin consists of a tetracyclic ring, with the sugar daunosamine attached by a glycosidic linkage. Structurally, doxorubicin is related to daunomycin (daunorubicin) and differs only in hydroxyl group substitution (instead of hydrogen) at the alkyl side chain, at position '9' of the 'A' ring.

Name and address

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