
NDC 67457-436-50
DOXOrubicin
Hydrochloride
for Injection, USP
50 mg/vial
CAUTION: CYTOTOXIC AGENT
LYOPHILIZED
For IV use only
Mylan
Rx only
Single-Dose Vial
DOXOrubicin
Hydrochloride
Mylan

INTRODUCTION:

- Doxorubicin belongs to anthracycline and antitumor antibiotic.
- Doxorubicin is a chemotherapy medication used to treat cancers like breast cancer ,bladder cancer, lymphoma and acute lymphocytic leukemia.
- FDA approved for use alone or in combination with other drugs.

Indications of Doxorubicin

❖FDA labeled indications:

- AIDS-related Kaposi's sarcoma.
- Multiple myeloma (In combination with bortezomib)
- Ovarian carcinoma.
- Non-Hodgkin's lymphoma, Advanced
- Non-small cell lung cancer, Advanced
- Acute and chronic lymphoid leukemia
- Carcinoma of prostate, Advanced
- Carcinoma of stomach, Advanced

Contraindications

- Doxorubicin is contraindicated in patients with
  - Severe myocardial insufficiency
  - Recent myocardial infarction
  - Severe persistent drug-induced myelosuppression
  - Severe hepatic impairment
  - Hypersensitivity to doxorubicin

Doxorubicin – "Red Death"

- **Dose:** 20-30 mg/m^2 IV over 20 minutes, q2-3 weeks
  - Premedicate with diphenhydramine and Cerenia
  - 1 mg/kg if less than 15 kg
- **Indications:** LSA, leukemia, carcinomas, sarcomas
- **Unique Side Effects:**
  - Severe necrosis leading to amputation or death due to cardiotoxicity if extravasated
  - More likely to cause GI signs and malaise than the other drugs in CHOP protocols
    - Often the last drug to lose effectiveness in CHOP
  - Toxicity can be somewhat cumulative – may need to reduce dose with time
  - Prolonged myelosuppression – check CBC at 10 days post Tx

important information

- Due to these **side effects** and its **red colour**, doxorubicin has earned the nickname **"red devil "or "red death.“**

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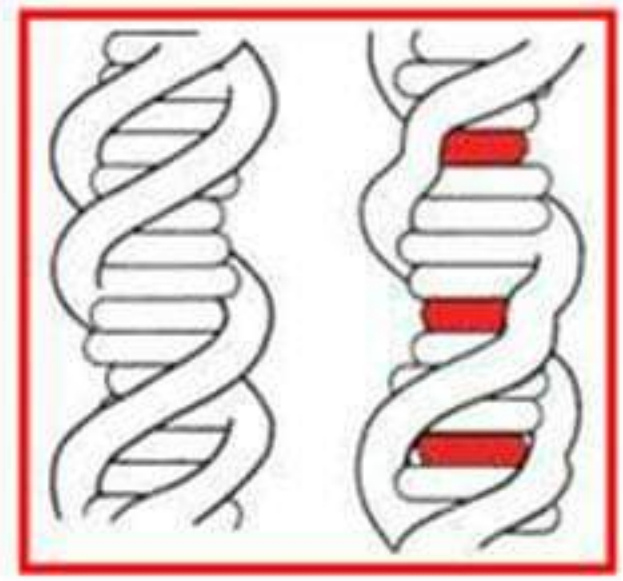
Doxorubicin: mechanism of action

- DNA intercalation: binding to DNA, inhibit the progression of topoisomerase II which unwinds DNA for transcription, consequent in cell cycle disruption & cell death
- Free radical damage involving reactive oxygen species (ROS) ⟶ ss breakage



Mode Of Action (continue)

- Furthermore, doxorubicin can affect the cell membrane directly by binding to plasma proteins causing enzymatic electron reduction of doxorubicin.

This can cause the formation of highly reactive species of hydroxyl free radicals. Free radicals are responsible for the dangerous side effects of toxicity elicited by the drug's use, though these same mechanisms make doxorubicin a potent anticancer drug, allowing be efficacious against various forms of cancer.

Dose Adjustments

- Cardiac impairment
  - Discontinue doxorubicin in patients who develop signs or symptoms of cardiomyopathy
- Hepatic impairment
  - Doxorubicin is contraindicated in patients with severe hepatic impairment
  - Decrease the dose in patients with elevated serum total bilirubin concentrations as follows

Serum bilirubin concentration	Doxorubicin dose reduction
1.2 – 3 mg/dL	50%
3.1 – 5 mg/dL	75%
>5 mg/dL	Do not initiate / Discontinue

Doxorubicin

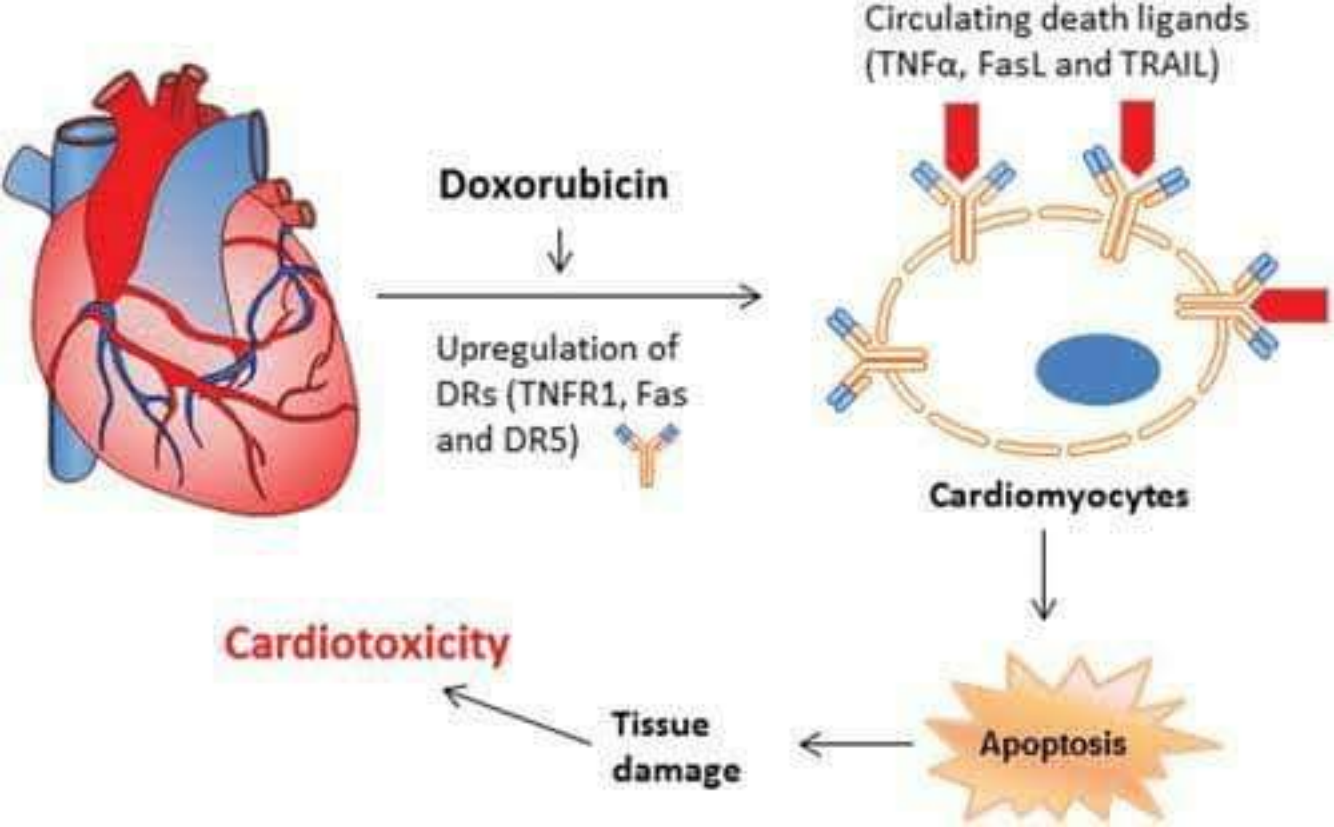
- Therapy routine for Breast Cancer, ovary, prostate, stomach, thyroid; small cell cancer of lung, liver; squamous cell cancer of head and neck; multiple myeloma, Hodgkin's disease, lymphomas, ALL, AML
- 60-75 mg/m^2 IV q21Days OR
- 60 mg/m^2 IV q14Days OR
- 40-60 mg/m^2 IV q21-28Days OR
- 20 mg/m^2/dose qweek

Adverse Effects

- Most frequently reported adverse reactions
  - Alopecia,
  - Esophagitis
  - Infection
  - Leukopenia
  - Nausea
  - Stomatitis
  - Urine or tear discoloration
  - Vomiting

Adverse Effects (continued)

- Rare adverse effects
  - Allergic dermatitis
  - Allergic reactions
  - Anaphylaxis
  - Bronchospastic pulmonary disease
  - Cardiotoxicity
  - Drug fever
  - Dyspnea
  - Extravasation injury
  - Myelodysplastic syndrome
  - Pruritus of skin
  - Severe bone marrow depression
  - Skin rash
  - Urticaria
  - Wheezing


Circulating death ligands
(TNFα, FasL and TRAIL)
Doxorubicin
Upregulation of
DRs (TNFR1, Fas
and DR5)
Cardiomyocytes
Apoptosis
Tissue
damage
Cardiotoxicity

DRUG NAME: Doxorubicin

SYNONYM(S): ADR,[1] Adria,[2] Dox,[2] hydroxyl daunorubicin,[2] NSC-123127[2]

COMMON TRADE NAME(S): generic available,[3] ADRIAMYCIN®,[4] RUBEX®[5] (USA)

CLASSIFICATION: anthracycline antineoplastic antibiotic[6]

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Doxorubicin binds directly to DNA via intercalation between base pairs on the DNA helix.[2] Doxorubicin also inhibits DNA repair by inhibiting topoisomerase II. These actions result in the blockade of DNA and RNA synthesis and fragmentation of DNA.[2] Doxoubicin is also a powerful iron-chelator. The iron-doxorubicin complex can bind DNA and cell membranes producing free radicals that immediately cleave DNA and cell membranes. Although maximally cytotoxic in S phase, doxorubicin is not cell cycle-specific.[2]

PHARMACOKINETICS:

Interpatient variability	clearance reduced in obese patients (i.e., >130% ideal body weight)[2,7]	
Oral Absorption	not stable in gastric acids; not absorbed from GI tract	
Distribution	widely distributed in plasma and in tissues	
	cross blood brain barrier?	no
	volume of distribution[4]	25 L/kg
	plasma protein binding[4]	70%
Metabolism	in the liver and other tissues by an aldo-keto reductase enzyme	
	active metabolite	doxorubicinol
	inactive metabolite(s)	doxorubicinone, aglycones and conjugates
Excretion	predominantly in bile	
	urine[4]	3-10% as metabolites
	feces[4]	40-50% as unchanged drug
	terminal half life[8]	20-48 h
	clearance[9]	27.5-59.6 L/h/m^2
Gender	terminal half life[4]: male 54 h; female 35 h	
	clearance[4]: male 113 L/h; female 44 L/h	
Children	increased risk for delayed cardiotoxicity[4]	

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:

*Bladder carcinoma
*Breast cancer
Endocrine carcinoma[10]
Ewing's sarcoma[12,13]
*Gastric cancer
*Gynecological carcinoma
*Head and neck cancer
*Hepatic carcinoma
Hepatoma[14]
Kaposi's sarcoma[15]
*Leukemia, acute lymphoblastic
*Leukemia, acute myeloblastic
*Lung cancer
*Lymphoma, Hodgkin's
*Lymphoma, non-Hodgkin's
*Neuroblastomas
Osteosarcoma[16,17]
Pancreatic cancer[18]
*Sarcoma, soft tissue
*Testicular carcinoma
*Thyroid carcinoma
Urothelial carcinoma[19]
*Wilm's tumour

*Health Canada approved indication

Other uses:

Multiple myeloma[6]
Prostate cancer[6]
Thymoma[11]

SPECIAL PRECAUTIONS:

Contraindicated in patients with the following conditions[4,7]:

- hypersensitivity to doxorubicin, anthracyclines (e.g., epirubicin, daunorubicin), or anthracenediones (e.g., mitoxantrone, mitomycin)
- previous therapy with high cumulative doses of anthracyclines (e.g., doxorubicin, daunorubicin, epirubicin, idarubicin) or some anthracenediones (e.g., mitoxantrone)
- severe hepatic impairment
- severe myocardial insufficiency or recent myocardial infarction, severe arrhythmias, or history of severe cardiac disease

Cardiac toxicity is a risk of doxorubicin therapy that may be manifested by early (acute) or late (delayed) effects.[20] Cardiac function should be assessed at baseline and continue during treatment. Risk factors for developing doxorubicin-induced cardiotoxicity include:[3,7,20-23]

- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease
- extremes of age
- liver disease
- concomitant chemotherapy, especially bevacizumab, cyclophosphamide, PACLitaxel, and trastuzumab
- concomitant use of drugs that can suppress cardiac contraction
- whole body hyperthermia
- female gender (mainly in children)

Carcinogenicity: Doxorubicin is carcinogenic in animals and is potentially carcinogenic in humans.[11]

Mutagenicity: Mutagenic in the Ames test.[3] Doxorubicin is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[7]

Fertility: Treatment with doxorubicin may produce gonadal suppression, resulting in amenorrhea or azoospermia.[11]

Pregnancy: Doxorubicin is classed as FDA Pregnancy Category D.[24] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk. Chemotherapy protocols including doxorubicin have been administered during pregnancy to treat breast cancer.[25] For more information, refer to BC Cancer's Cancer Management Guidelines *Breast Cancer in Pregnancy*.

Breastfeeding should not occur while a mother is undergoing chemotherapy with doxorubicin because Doxorubicin is secreted into breast milk.[3,4]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	anaphylaxis may occur
	fever, chills and urticaria (occasionally)
blood/bone marrow/ febrile neutropenia	myelosuppression; especially leukopenia (75%)[4] reaching nadir 10-14 days after treatment; recovery usually by day 21
cardiovascular (arrhythmia)	acute arrhythmia (0.5-3%)[26,27]; see paragraph following **Side Effects** table
cardiovascular (general)	acute transient ECG changes (20-30%)[27]; see paragraph following **Side Effects** table
	delayed/late cardiotoxicity (18-65%)[28]; risk increases steeply with higher cumulative doses[28]; see paragraph following **Side Effects** table
	phlebosclerosis
dermatology/skin	*extravasation hazard: vesicant*[29]
	complete alopecia (up to 100%), regrowth occurs 2-3 months after discontinuing doxorubicin therapy[6]
	facial flushing, if given too rapidly
	hyperpigmentation of nail beds and dermal creases, soles, palms (1-10%)[4,8]
	photosensitivity[7]
	radiation recall reaction (hypersensitivity to irradiated skin); including redness, warmth, erythema and dermatitis in the radiation port (<1%)[4,6]
endocrine	amenorrhea, hot flashes, oligospermia, azoospermia
gastrointestinal	*emetogenic potential: dose-related*[30-33]*: high-moderate for > 60 mg/m^2, low-moderate for 20-60 mg/m^2, low for < 20 mg/m^2*
	anorexia (>10%)[4]
	diarrhea (>10%)[4]
	mucositis; stomatitis and esophagitis (>10%)[4]
	nausea and vomiting (21-55%)[4]; dose related

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	ulceration and necrosis of colon (>10%)[4]
hepatic	changes in transaminase levels[7]
metabolic/laboratory	hyperuricemia secondary to rapid tumour lysis of neoplastic cells, particularly when used in leukemia (1-10%)[4]
ocular/visual	conjunctivitis and lacrimation (rarely)
renal/genitourinary	red colouration of urine for 1-2 days after administration (>10%)[4]
secondary malignancy	secondary acute myelogenous leukemia,[4] acute lymphocytic leukemia[7]
	pediatric patients are at increased risk for developing later neoplastic disease (<1%)[4]
sexual/reproductive function	gonadal suppression resulting in amenorrhea or azoospermia[11]

Adapted from standard reference[3] unless specified otherwise.

Hyperuricemia may result from cell lysis by doxorubicin and may lead to electrolyte disturbances or acute renal failure.[34] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[35]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH>7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[36] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminum hydroxide (AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminum hydroxide has been added, discontinue sodium bicarbonate.[37]

Cardiotoxicity is thought to be due to free radical damage as myocardial tissue is susceptible to these highly reactive species.[38] Anthracycline cardiotoxicity may present with early or late effects.[39,40] The following information applies to all anthracyclines, anthracenediones and mitoxantrone.[20,38,40]

Early cardiotoxic effects are not dose-related and may present from mild ECG changes to life-threatening arrhythmias.[20,38,39] These events may occur during or immediately after a single dose of anthracycline treatment,[20,38] but do not predict subsequent development of delayed cardiotoxicity and are not considered indications for suspension of therapy.[3,20,22,38,39,41]

Late cardiotoxic effects, which are dose-related and clinically the most important type of cardiotoxic effect, present as reduced LVEF or symptomatic CHF, and typically occur weeks to years after completion of treatment.[3,20,22,38,40] Abnormalities in LVEF are associated with all the anthracyclines and their derivatives.[40] LVEF changes are related to the total cumulative dose, are irreversible and refractory to medical therapy.[23,38]

Prevention and treatment: Cardiac assessment should occur at baseline and throughout therapy. Monitor for symptomatic congestive heart failure (CHF) or reduced left ventricular ejection fraction (LVEF). Sensitive, non-invasive methods to measure LVEF include radionucleotide angiography (RNA), MUGA, or echocardiogram.[40] Late cardiotoxic effects may be prevented by stopping treatment with the associated anthracycline once patients have reached the suggested maximum cumulative dose.[23,38] Management of anthracycline cardiotoxicity includes discontinuation of the drug and initiating standard treatment of CHF.[40]

Cardiotoxicity risk can be reduced but not eliminated with the use of alternative anthracyclines (i.e., epirubicin or liposomal doxorubicin) or by altering the frequency of administration (once a week vs. once every 3 weeks, or continuous infusion).[40] Cardioprotectant therapy with dexrazoxane may be considered for patients with cumulative doxorubicin-equivalent doses greater than 300 mg/m^2.[20,42,43]

Cumulative doses should be calculated using the following table, taking into account all previous anthracyclines or anthracenediones received during the patient's lifetime.

AGENT	SUGGESTED **CONVERSION FACTOR** TO **DOXORUBICIN DOSE**[44-46]*	SUGGESTED **MONITORING THRESHOLD**[40,47-53]**
DAUNOrubicin	x 0.5-0.83	450 mg/m^2
DOXOrubicin	x 1	300 mg/m^2
epirubicin	x 0.5-0.67	600 mg/m^2
IDArubicin	x 2-5	150 mg/m^2
mitoXANTRONE	x 2.2-4	140 mg/m^2

* based on relative hematological toxicities[45]

** Treatment may continue beyond these doses in selected patients, if the clinician has considered the potential risks and benefits. The addition of dexrazoxane may be considered, and monitoring should be increased. Maximum tolerated doses are variable; some patients may tolerate doxorubicin equivalent doses exceeding 1000 mg/m^2 while other patients exhibit symptomatic CHF at doxorubicin equivalent doses less than 300 mg/m^2.

Local effects: Extravasation of doxorubicin can occur with or without accompanying stinging or burning sensation, and even if blood returns well on aspiration of the infusion needle.[3] Extravasation of doxorubicin will result in severe ulceration and soft tissue necrosis.[4] To minimize the risk of thrombosis or perivenous extravasation, the dose should be infused over 3 to 10 minutes, depending on the vein size and the dose.[7] For more information on prevention and treatment of extravasation with doxorubicin, refer to BC Cancer Policy III-20 *Prevention and Management of Extravasation of Chemotherapy*. Also, monitor for local erythematous streaking along vein and/or facial flushing which may indicate a too rapid infusion rate.[4] This has traditionally been called the "doxorubicin flare."[54,55]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
barbiturates[56] (e.g., phenobarbital)	delayed, moderate possible; decreased pharmacological effects of doxorubicin	doxorubicin metabolism increased by barbiturates via CYP3A4 induction	monitor therapy
bevacizumab[21]	doxorubicin-induced cardiotoxicity may be increased	unknown	monitor for increased cardiotoxicity (e.g., congestive heart failure)
calcium channel blockers[7] (e.g., verapamil)[4]	doxorubicin-induced cardiotoxicity may be increased	additive toxicity	monitor cardiac function throughout treatment
cyclophosphamide[4]	doxorubicin-induced cardiotoxicity may be increased	additional myocardial cell damage	caution, but combination regime is commonly used
cyclophosphamide[3]	cyclophosphamide-induced hemorrhagic cystitis may be increased	unknown	caution

AGENT	EFFECT	MECHANISM	MANAGEMENT
cyclosporine[57]	increased pharmacological effects of doxorubicin	doxorubicin metabolism decreased by cyclosporine either by competition for CYP3A4 or p-glycoprotein inhibition	consider therapy modification
digoxin tablets[58]	delayed, moderate, suspected; decreased pharmacological effects of digoxin	digoxin absorption decreased by antineoplastic agents due to alteration of intestinal mucosa	monitor for decreased effect of digoxin
mercaptopurine[4]	increased mercaptopurine hepatotoxicity[3]	unknown	monitor therapy
paclitaxel[59]	increased doxorubicin pharmacological effects[4]	doxorubicin clearance decreased either by competition for CYP3A4 or p-glycoprotein	monitor for increased cardiotoxicity (e.g., congestive heart failure)or consider using docetaxel instead of paclitaxel[59]
quinolones[56] (e.g., ciprofloxacin)	delayed, moderate, possible; the antimicrobial effect of quinolones may be decreased	quinolone absorption decreased by antineoplastic agents due to alteration of intestinal mucosa	monitor therapy
stavudine[60]	decreased pharmacological effects of stavudine	stavudine metabolism to active drug is decreased by doxorubicin due to inhibition of phosphorylation	avoid concomitant use
streptozocin[4]	greatly enhanced leukopenia and thrombocytopenia	doxorubicin half life possibly prolonged[11]	caution
trastuzumab[61]	increased cardiotoxicity	unknown	consider therapy modification

Doxorubicin is a major CYP2D6 substrate therefore drugs that are CYP2D6 inhibitors (e.g., chlorpromazine, paroxetine, quinine) could potentially increase the pharmacological effects of doxorubicin.[4] Doxorubicin is a major CYP3A4 substrate therefore drugs that are CYP3A4 inducers (e.g., carbamazepine, phenytoin, St John's wort) could potentially decrease the pharmacological effects of Doxorubicin.[4] CYP3A4 inhibitors (e.g., diclofenac, imatinib, verapamil) could potentially increase the pharmacological effects of Doxorubicin.[4]

Doxorubicin is a moderate CYP2B6 inhibitor therefore could potentially increase the pharmacological effects of drugs that are CYP2B6 substrates (e.g., promethazine, propofol, selegiline).[4] Doxorubicin is also a weak CYP2D6 inhibitor and a weak CYP3A4 inhibitor.[4]

PARENTERAL ADMINISTRATION:

	BC Cancer administration guideline noted in ***bold, italics***
Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
Direct intravenous	***peferred method*** due to need for frequent monitoring for signs of extravasation: via small (21 or 23) gauge needle into tubing of running IV. ***Push slowly***, so that drip of IV solution does not stop or reverse. Check for blood return before administration and after every 2-3 mL of drug. If no blood return, stop the injection and assess the IV site. Flush with 20 mL NS or D5W after administration to clear any remaining drug from tubing.
Intermittent infusion[62-67]	has been used
Continuous infusion[3]	has been used
Intraperitoneal	***hyperthermic intraperitoneal chemotherapy (HIPEC):*** pump solution into abdominal cavity and circulate as per protocol using hyperthermia pump; solutions and dwell time vary by protocol[68,69]
Intrapleural[2]	has been used
Intrathecal	no information found
Intra-arterial[2,3]	has been used
Intravesical[70,71]	induction doses of 50-80 mg in 50-100 mL NS have been used weekly for 4 weeks, followed by monthly maintenance doses for 1 year or longer; solutions are retained for 1-2 h after instillation

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	1 week[72]:	25 mg/m^2 IV for one dose on day 1 (total dose per cycle 25 mg/m^2)
	2	***15-20 mg IV for one dose on day 1*** ***(total dose per cycle 15-20 mg)***
	2 weeks[73]:	***60 mg/m^2 IV for one dose on day 1*** ***(total dose per cycle 60 mg/m^2)***
	3 weeks[10,16-18,73-94]:	***40-75 mg/m^2 IV for one dose on day 1*** ***(total dose per cycle 40-75 mg/m^2)***
	4 weeks[95]:	***50 mg/m^2 IV for one dose on day 1*** ***(total dose per cycle 50 mg/m^2)***
	4 weeks[96]:	***30 mg/m^2 IV for one dose on day 2*** ***(total dose per cycle 30 mg/m^2)***
	4 weeks[97]:	***30 mg/m^2 IV for one dose on days 1 and 8*** ***(total dose per cycle 60 mg/m^2)***
	4 weeks[98,99]:	***25-30 mg/m^2 IV for one dose on days 1 and 15*** ***(total dose per cycle 50-60 mg/m^2)***
	6 weeks[12,13]:	***75 mg/m^2 IV for one dose on day 1*** ***(total dose per cycle 75 mg/m^2)***
	8 weeks[91]:	***50 mg/m^2 IV for one dose on day 1*** ***(total dose per cycle 50 mg/m^2)***
Suggested maximum cumulative dose[48]:	3 week cycle: 550 mg/m^2 1 week cycle: 700 mg/m^2	
	If risk factors are present: 3 week cycle: 400-450 mg/m^2 1 week cycle: 550 mg/m^2	
Concurrent radiation:	not recommended[72]; however in the BC Cancer Agency Protocol SAAJA,[93] selected patients may receive	
Dosage in obese patients[7]:	consider lower starting doses or longer intervals between cycles	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	
Dosage in renal failure:	no adjustment required[4]	

Dosage in hepatic failure:

suggested guidelines[4]

ALT/AST		Bilirubin (micromol/L)	Dose
2-3 x ULN		-	75%
> 3 x ULN	or	20-50	50%
-		51-85	25%
-		> 85	do not administer

Dosage in dialysis:

hemodialysis[4]: supplemental dose not required

chronic ambulatory peritoneal dialysis (CAPD)[100]: no data

continuous arteriovenous or venovenous hemofiltration (CAVH)[100]: dose for GFR 10-50 mL/min

Children:

Intravenous[1]:

Cycle Length:	
N/A	45-90 mg/m^2 IV continuous infusion (24-96 h)
N/A	30-45 mg/m^2 IV daily x 3 or weekly
1 week:	20-30 mg/m^2 IV for one dose on day 1 (total dose per cycle 20-30 mg/m^2)
3 weeks:	40-75 mg/m^2 IV for one dose on day 1 (total dose per cycle 40-75 mg/m^2)