DRUG NAME: Doxorubicin

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

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

CLASSIFICATION: anthracycline antineoplastic antibiotic [5]

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. [3] Doxorubicin 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) [2,6]	
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 [3]	25 L/kg
	plasma protein binding [3]	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 [3]	3-10% as metabolites
	feces [3]	40-50% as unchanged drug
	terminal half life [7]	20-48 h
	clearance [8]	27.5-59.6 L/h/m^2
Gender	terminal half life [3]: male 54 h; female 35 h	
	clearance [3]: male 113 L/h; female 44 L/h	
Children	increased risk for delayed cardiotoxicity [3]	

Adapted from standard reference [9] unless specified otherwise.

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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

Other uses:

Multiple myeloma [5]
Prostate cancer [5]
Thymoma [11]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to doxorubicin, anthracyclines (e.g., epirubicin, daunorubicin), or anthracenediones (e.g., mitoxantrone, mitomycin) [3,6]
- previous therapy with high cumulative doses of anthracyclines (e.g., doxorubicin, daunorubicin, epirubicin, idarubicin) or some anthracenediones (e.g., mitoxantrone) [3,6]
- severe myocardial insufficiency or recent myocardial infarction, severe arrhythmias, or history of severe cardiac disease [3,6]

Caution:

- risk factors for developing doxorubicin-induced ***cardiotoxicity*** include: [6,9,20-23]
  - 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)

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Carcinogenicity: Secondary leukemia (with or without a preleukemic phase) has been reported in patients treated with topoisomerase-II inhibitors, including anthracyclines such as doxorubicin. Secondary leukemia is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents, is used in patients heavily pretreated with cytotoxic drugs, or when doses of the anthracycline have been escalated and/or used in combination with radiation. Secondary leukemia can have a 1 to 3 year latency period, and can occur as late as 10 years following treatment. Pediatric patients are at risk of developing secondary acute myelogenous leukemia (AML).[24]

Mutagenicity: Mutagenic in the Ames test. [9] Doxorubicin is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests. [6]

Fertility: In women, doxorubicin may cause amenorrhea, resulting in infertility during the time of drug administration. Ovulation and menstruation appear to return to normal after termination of treatment, although premature menopause has also occurred. Doxorubicin can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent. In some cases, sperm counts have been reported to return to normospermic levels; however, this may not occur for several years after the end of therapy. In animal studies, doxorubicin was found to be toxic to male reproductive organs, causing testicular atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia. Fertility preservation should be considered for male and female patients of reproductive potential.[24]

Pregnancy: In animal studies, when doxorubicin was administered during organogenesis, an increased incidence of fetal resorption and increased fetal skeletal and soft tissue malformations were observed. Doxorubicin was also shown to block implantation and act as an abortifacient. Doxorubicin has been implicated in causing fetal harm when administered to pregnant women. Contraception is recommended for female patients of reproductive potential during treatment and for at least 6.5 months after the last dose. For male patients with female partners of reproductive potential, contraception is recommended during treatment and for at least 3.5 months after the last dose.[24] Chemotherapy protocols including doxorubicin have been administered during pregnancy to treat breast cancer.[25] For more information, refer to BC Cancer's Cancer Management Manual/Breast Cancer ***Special Circumstances: Breast Cancer in Pregnancy***.

Breastfeeding should not occur while a mother is undergoing chemotherapy with doxorubicin because doxorubicin is secreted into breast milk. [3,9]

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%) [3] 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%) [26]; risk increases steeply with higher cumulative doses [28]; see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	phlebosclerosis
dermatology/skin	*extravasation hazard:* vesicant [29]
	complete alopecia (up to 100%), regrowth occurs 2-3 months after discontinuing doxorubicin therapy [5]
	facial flushing, if given too rapidly
	hyperpigmentation of nail beds and dermal creases, soles, palms (1-10%) [3,7]
	photosensitivity [6]
	radiation recall reaction (hypersensitivity to irradiated skin); including redness, warmth, erythema and dermatitis in the radiation port (<1%) [3,5]
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%) [3]
	diarrhea (>10%) [3]
	mucositis; stomatitis and esophagitis (>10%) [3]
	nausea and vomiting (21-55%) [3]; dose related
	ulceration and necrosis of colon (>10%) [3]
hepatic	changes in transaminase levels [6]
metabolic/laboratory	hyperuricemia secondary to rapid tumour lysis of neoplastic cells, particularly when used in leukemia (1-10%) [3]
ocular/visual	conjunctivitis and lacrimation (rarely)
renal/genitourinary	red colouration of urine for 1-2 days after administration (>10%) [3]
secondary malignancy	secondary acute myelogenous leukemia, [3] acute lymphocytic leukemia [6]
	pediatric patients are at increased risk for developing later neoplastic disease (<1%) [3]
sexual/reproductive function	gonadal suppression resulting in amenorrhea or azoospermia [11]

Adapted from standard reference [9] 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

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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. [22,38,40]

Early cardiotoxic effects are not dose-related and may present from mild ECG changes to life-threatening arrhythmias. [22,38,39] These events may occur during or immediately after a single dose of anthracycline treatment, [22,38] but do not predict subsequent development of delayed cardiotoxicity and are not considered indications for suspension of therapy. [9,21,22,38,39,41]

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. [9,21,22,38,40] 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. [22,42,43]

Cumulative doses should be calculated and account for all previous anthracyclines or anthracenediones received during the patient's lifetime. For further information on suggested conversion factors and monitoring thresholds for anthracyclines, see ***Dose Conversion for Anthracyclines Exposure*** in Appendix.

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. [9] Extravasation of doxorubicin will result in severe ulceration and soft tissue necrosis. [3] 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. [6] For more information on prevention and treatment of extravasation with doxorubicin, refer to BC Cancer Systemic Therapy 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. [3] This has traditionally been called the "doxorubicin flare." [44,45]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
barbiturates [46] (e.g., phenobarbital)	delayed, moderate possible; decreased pharmacological effects of doxorubicin	doxorubicin metabolism increased by barbiturates via CYP3A4 induction	monitor therapy
bevacizumab [20]	doxorubicin-induced cardiotoxicity may be increased	unknown	monitor for increased cardiotoxicity (e.g., congestive heart failure)
calcium channel blockers [6] (e.g., verapamil) [3]	doxorubicin-induced cardiotoxicity may be increased	additive toxicity	monitor cardiac function throughout treatment

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AGENT	EFFECT	MECHANISM	MANAGEMENT
cyclophosphamide [3]	doxorubicin-induced cardiotoxicity may be increased	additional myocardial cell damage	caution, but combination regime is commonly used
cyclophosphamide [9]	cyclophosphamide-induced hemorrhagic cystitis may be increased	unknown	caution
cyclosporine [47]	increased pharmacological effects of doxorubicin	doxorubicin metabolism decreased by cyclosporine either by competition for CYP3A4 or p-glycoprotein inhibition	consider therapy modification
digoxin tablets [48]	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 [3]	increased mercaptopurine hepatotoxicity [9]	unknown	monitor therapy
paclitaxel [49]	increased doxorubicin pharmacological effects [3]	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 [49]
quinolones [46] (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 [50]	decreased pharmacological effects of stavudine	stavudine metabolism to active drug is decreased by doxorubicin due to inhibition of phosphorylation	avoid concomitant use
streptozocin [3]	greatly enhanced leukopenia and thrombocytopenia	doxorubicin half life possibly prolonged [11]	caution
trastuzumab [51]	increased cardiotoxicity	unknown	consider therapy modification

Doxorubicin is a major CYP2D6 substrate therefore drugs that are CYP2D6 inhibitors could potentially increase the pharmacological effects of doxorubicin. [3] Doxorubicin is a major CYP3A4 substrate therefore drugs that are CYP3A4 inducers could potentially decrease the pharmacological effects of Doxorubicin. [3] CYP3A4 inhibitors could potentially increase the pharmacological effects of Doxorubicin. [3]

Doxorubicin is a moderate CYP2B6 inhibitor therefore could potentially increase the pharmacological effects of drugs that are CYP2B6 substrates. [3] Doxorubicin is also a weak CYP2D6 inhibitor and a weak CYP3A4 inhibitor. [3]

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SUPPLY AND STORAGE:

***Injection*:**
Accord Healthcare Inc. supplies doxorubicin as 10 mg, 50 mg, and 200 mg ready-to-use, single-use (preservative free) vials in a concentration of 2 mg/mL. Refrigerate. Protect from light.[24]

Pfizer Canada ULC supplies doxorubicin as 10 mg and 50 mg ready-to-use, single-use (preservative free) vials in a concentration of 2 mg/mL. Refrigerate. Protect from light.[52]

Teva Canada Limited supplies doxorubicin as 10 mg, 50 mg, and 200 mg ready-to-use, single-use (preservative free) vials in a concentration of 2 mg/mL. Refrigerate. Protect from light.[53]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information: Aluminum metal interacts with doxorubicin solution producing a darker colour solution and a possible precipitation of drug. [4] Aluminum-containing apparatus should not be used in the preparation or administration of doxorubicin. [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	over 3-10 min [24] into tubing of running IV; see ***Systemic Therapy Policy III-20: Prevention and Management of Extravasation of Chemotherapy***
Intermittent infusion [54-59]	has been used
Continuous infusion [9]	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 [60,61]
Intrapleural [2]	has been used
Intrathecal	no information found
Intra-arterial [2,9]	has been used
Intravesical [62,63]	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

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DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

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

	Cycle Length:	
Intravenous:	1 week [64]:	25 mg/m^2 IV for one dose on day 1 (total dose per cycle 25 mg/m^2)
	1 week [65]***:***	***15-20 mg IV for one dose on day 1*** ***(total dose per cycle 15-20 mg)***
	2 weeks [66]***:***	***60 mg/m^2 IV for one dose on day 1*** ***(total dose per cycle 60 mg/m^2)***
	3 weeks [10,16-18,66-87]***:***	***40-75 mg/m^2 IV for one dose on day 1*** ***(total dose per cycle 40-75 mg/m^2)***
	4 weeks [88]***:***	***50 mg/m^2 IV for one dose on day 1*** ***(total dose per cycle 50 mg/m^2)***
	4 weeks [89]***:***	***30 mg/m^2 IV for one dose on day 2*** ***(total dose per cycle 30 mg/m^2)***
	4 weeks [90]***:***	***30 mg/m^2 IV for one dose on days 1 and 8*** ***(total dose per cycle 60 mg/m^2)***
	4 weeks [91,92]***:***	***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 [84]***:***	***50 mg/m^2 IV for one dose on day 1*** ***(total dose per cycle 50 mg/m^2)***
Suggested maximum cumulative dose [24,52,53]*:*	3 week cycle: 550 mg/m^2 1 week cycle: 700 mg/m^2	
Concurrent radiation:	not recommended [64]; has been given concurrently in selected protocols[93]	
Dosage in obese patients [6]*:*	consider lower starting doses or longer intervals between cycles	

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

Dosage in myelosuppression:

Cycle Length:
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 [3]

Dosage in hepatic failure:

suggested guidelines [3]

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 [3]: supplemental dose not required

chronic ambulatory peritoneal dialysis (CAPD) [94]: no data

continuous arteriovenous (CAVH) or venovenous hemofiltration (CVVH) [94]: 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)

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