

## Doxorubicin (conventional): Drug information

Copyright 1978-2017 Lexicomp, Inc. All rights reserved.

(For additional information [see "Doxorubicin \(conventional\): Patient drug information"](#) and [see "Doxorubicin \(conventional\): Pediatric drug information"](#))

For abbreviations and symbols that may be used in Lexicomp ([show table](#))

### ALERT: US Boxed Warning

#### Experienced physician:

Doxorubicin should be administered only under the supervision of a health care provider who is experienced in the use of cancer chemotherapeutic agents.

#### Extravasation:

Extravasation of doxorubicin can result in severe local tissue injury and necrosis requiring wide excision of the affected area and skin grafting. Immediately terminate the drug and apply ice to the affected area. Doxorubicin must not be given by the intramuscular (IM) or subcutaneous route.

#### Cardiotoxicity:

Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure (CHF) may occur during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function based on a combined index of signs, symptoms, and decline in left ventricular ejection fraction (LVEF) is estimated to be 1% to 2% at a total cumulative dose of 300 mg/m<sup>2</sup>, 3% to 5% at 400 mg/m<sup>2</sup>, 5% to 8% at 450 mg/m<sup>2</sup>, and 6% to 20% at 500 mg/m<sup>2</sup>. The risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 400 mg/m<sup>2</sup>. Risk factors (active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other cardiotoxic drugs) may increase the risk of cardiac toxicity. Cardiac toxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present. Pediatric patients are at an increased risk for developing delayed cardiotoxicity.

#### Secondary malignancy:

Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome have been reported in patients treated with doxorubicin. The occurrence of refractory secondary AML or myelodysplastic syndrome is more common when anthracyclines are given in combination with DNA-damaging antineoplastic agents or radiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. Pediatric patients are also at risk of developing secondary AML.

## Hepatic function impairment:

The dosage should be reduced in patients with impaired hepatic function.

## Myelosuppression:

Severe myelosuppression, resulting in serious infection, septic shock, requirement for transfusions, hospitalization, and death, may occur.

**Brand Names: US** Adriamycin

**Brand Names: Canada** Adriamycin PFS; Doxorubicin Hydrochloride For Injection, USP; Doxorubicin Hydrochloride Injection

**Pharmacologic Category** Antineoplastic Agent, Anthracycline; Antineoplastic Agent, Topoisomerase II Inhibitor

**Dosing: Adult** Doxorubicin is associated with a moderate to high emetic potential (depending on dose or regimen); antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Roila 2016).

**Manufacturer's labeling: Note:** Lower dosages should be considered for patients with inadequate marrow reserve (due to advanced age, prior treatment, or neoplastic marrow infiltration). Cumulative doses above 550 mg/m<sup>2</sup> are associated with an increased risk of cardiomyopathy.

**Breast cancer:** IV: 60 mg/m<sup>2</sup> on day 1 of a 21-day cycle (in combination with cyclophosphamide) for 4 cycles

**Metastatic solid tumors, leukemia, or lymphoma:** IV:

Single-agent therapy: 60 to 75 mg/m<sup>2</sup> every 21 days

Combination therapy: 40 to 75 mg/m<sup>2</sup> every 21 to 28 days

## Indication-specific dosing (off-label dosing):

**Acute lymphoblastic leukemia:** IV:

*Hyper-CVAD regimen:* 50 mg/m<sup>2</sup> on day 4 of Courses 1, 3, 5, and 7 (in combination with cyclophosphamide, vincristine, and dexamethasone); alternating cycles with high-dose methotrexate and cytarabine (Kantarjian 2004)

*CALGB 8811 regimen:* 30 mg/m<sup>2</sup> on days 1, 8 and 15 of late intensification (Course IV; 8-week cycle); in combination with vincristine, dexamethasone, cyclophosphamide, thioguanine, and cytarabine (Larson1995)

**Bladder cancer, transitional cell:** IV: *Dose-dense MVAC regimen:* 30 mg/m<sup>2</sup> on day 2 every 14 days (in combination with methotrexate, vinblastine, and cisplatin) (Sternberg 2001)

**Breast cancer:** IV:

*CAF regimen:* 30 mg/m<sup>2</sup> on days 1 and 8 every 28 days for 6 cycles (in combination with cyclophosphamide and fluorouracil) (Bull 1978)

*FAC regimen:* 50 mg/m<sup>2</sup> on day 1 (or administered as a 72-hour continuous infusion) every 21 days for 6 cycles (in combination with fluorouracil and cyclophosphamide) (Assikis 2003)

*TAC regimen:* 50 mg/m<sup>2</sup> on day 1 every 21 days for 6 cycles (in combination with docetaxel and cyclophosphamide) (Martin 2005)

#### **Ewing sarcoma: IV:**

*VAC/IE regimen:* Adults ≤30 years: 75 mg/m<sup>2</sup> on day 1 every 21 days for 5 cycles (in combination with vincristine and cyclophosphamide; after 5 cycles, dactinomycin replaced doxorubicin), alternating cycles with ifosfamide and etoposide for a total of 17 cycles (Grier 2003)

*VAIA regimen:* Adults <35 years: 30 mg/m<sup>2</sup>/day on days 1 and 2 every 21 days (doxorubicin alternates with dactinomycin; in combination with vincristine and ifosfamide) for 14 cycles (Paulussen 2008)

*VIDE regimen:* 20 mg/m<sup>2</sup>/day over 4 hours on days 1 to 3 every 21 days for 6 cycles (in combination with vincristine, ifosfamide, and etoposide) (Juergens 2006)

#### **Hodgkin lymphoma: IV:**

*ABVD regimen:* 25 mg/m<sup>2</sup> on days 1 and 15 every 28 days (in combination with bleomycin, vinblastine, and dacarbazine) for 2 to 4 cycles (Bonadonna 2004; Engert 2010)

*BEACOPP and escalated BEACOPP regimens:* 25 mg/m<sup>2</sup> (BEACOPP) or 35 mg/m<sup>2</sup> (escalated BEACOPP) on day 1 every 21 days (in combination with bleomycin, etoposide, cyclophosphamide, vincristine, procarbazine, and prednisone) (Engert 2009)

*Stanford V regimen:* 25 mg/m<sup>2</sup> on weeks 1, 3, 5, 7, 9, and 11 of a 12-week cycle (in combination with mechlorethamine, vinblastine, vincristine, bleomycin, etoposide, and prednisone) (Horning 2002)

#### **Non-Hodgkin lymphoma: IV:**

*CHOP or RCHOP regimen:* 50 mg/m<sup>2</sup> on day 1 every 21 days (in combination with cyclophosphamide, vincristine, and prednisone +/- rituximab) (Coiffier 2010; McKelvey 1976)

*Hyper-CVAD + rituximab regimen:* 50 mg/m<sup>2</sup> administered as a continuous infusion over 24 hours on day 4 of Courses 1, 3, 5, and 7 (21-day treatment cycles; in combination with cyclophosphamide, vincristine, dexamethasone, and rituximab); alternating cycles with high-dose methotrexate and cytarabine (Thomas 2006)

*Dose-adjusted EPOCH or REPOCH regimen:* 10 mg/m<sup>2</sup>/day administered as a continuous infusion on days 1 to 4 every 21 days (in combination with etoposide, vincristine, cyclophosphamide, and prednisone +/- rituximab) (Garcia-Suarez 2007; Wilson 2002)

*Nordic regimen (Maxi-CHOP):* 75 mg/m<sup>2</sup> on day 1 every 21 days (in combination with cyclophosphamide, vincristine, prednisone, and rituximab), alternating cycles with high-dose cytarabine (Geisler 2008)

#### **Osteosarcoma: IV:**

*Cisplatin/doxorubicin regimen:* Adults ≤40 years: 25 mg/m<sup>2</sup> (bolus infusion) on days 1 to 3

every 21 days (in combination with cisplatin) (Bramwell 1992)

*High-dose methotrexate/cisplatin/doxorubicin/ifosfamide regimen: Adults <40 years:*

Preoperative: 75 mg/m<sup>2</sup> administered as a continuous infusion over 24 hours on day 3 of weeks 1 and 7 (in combination with methotrexate, cisplatin, and ifosfamide) (Bacci 2003)

Postoperative: 90 mg/m<sup>2</sup> administered as a continuous infusion over 24 hours on weeks 13, 22, and 31 (in combination with methotrexate, cisplatin, and ifosfamide) (Bacci 2003)

*High-dose methotrexate/cisplatin/doxorubicin regimen: Adults <40 years:*

Preoperative: 60 mg/m<sup>2</sup> over 8 hours on days 9 and 36 (in combination with methotrexate and cisplatin) (Bacci 2000)

Postoperative: 45 mg/m<sup>2</sup>/day over 4 hours for 2 consecutive days (in combination with methotrexate, cisplatin +/- ifosfamide, +/- etoposide; refer to protocol for criteria, frequency, and other specific information) (Bacci 2000)

**Small cell lung cancer, recurrent:** IV: *CAV regimen:* 45 mg/m<sup>2</sup> (maximum dose: 100 mg) on day 1 every 21 days (in combination with cyclophosphamide and vincristine) until disease progression or unacceptable toxicity or for at least 4 or 6 cycles past maximum response (von Pawel 1999)

**Soft tissue sarcoma:** IV:

**Nonspecific histologies:**

*AD regimen:* 60 mg/m<sup>2</sup> on day 1 every 21 days (either as a bolus infusion or administered continuously over 96 hours; in combination with dacarbazine) (Zalupski 1991)

*AIM regimen:* 30 mg/m<sup>2</sup> on days 1 and 2 every 21 days (in combination with ifosfamide and mesna) (Edmonson, 1993)

*MAID regimen:* 20 mg/m<sup>2</sup>/day as a continuous infusion on days 1 to 3 every 21 days (in combination with ifosfamide, mesna, and dacarbazine) (Elias 1989)

*Single-agent regimen:* 75 mg/m<sup>2</sup> on day 1 every 21 days until disease progression or unacceptable toxicity (Santoro 1995)

**Rhabdomyosarcoma:**

*VAC/IE regimen: Adults <21 years:* 37.5 mg/m<sup>2</sup> on days 1 and 2 (administered over 18 hours each day) every 6 weeks (in combination with vincristine and cyclophosphamide), alternating cycles with ifosfamide and etoposide (Arndt 1998)

*VAI regimen (based on a limited number of patients): Adults:* 25 mg/m<sup>2</sup>/day on days 1 to 3 every 21 days (in combination with vincristine and ifosfamide) (Ogilvie 2010)

**Off-label uses:**

**Endometrial carcinoma, advanced:** IV: 60 mg/m<sup>2</sup> on day 1 every 21 days for 8 cycles; maximum cumulative dose: 420 mg/m<sup>2</sup> (in combination with cisplatin) (Randall 2006)

**Multiple myeloma:** IV:

*PAD regimen: Induction:* 9 mg/m<sup>2</sup>/day on days 1 to 4 for 3 cycles (in combination with bortezomib and dexamethasone) (Sonneveld 2012)

*VDT-PACE regimen:* 10 mg/m<sup>2</sup>/day administered as a continuous infusion on days 1 to 4 of each cycle (in combination with bortezomib, dexamethasone, thalidomide, cisplatin, cyclophosphamide, and etoposide) (Lee 2003; Pineda-Roman 2008)

**Thymomas and thymic malignancies: IV:**

*CAP regimen:* 50 mg/m<sup>2</sup> on day 1 every 21 days for up to 8 cycles (in combination with cisplatin and cyclophosphamide) (Loehrer 1994)

*ADOC regimen:* 40 mg/m<sup>2</sup> on day 1 every 21 days (in combination with cisplatin, vincristine, and cyclophosphamide) (Fornasiero 1991)

**Uterine sarcoma:** IV: 60 mg/m<sup>2</sup> on day 1 every 21 days; maximum cumulative dose: 480 mg/m<sup>2</sup> (Omura, 1983) **or** 50 mg/m<sup>2</sup> (over 15 minutes) on day 1 every 21 days; maximum cumulative dose: 450 mg/m<sup>2</sup> (in combination with ifosfamide/mesna) (Sutton 1996)

**Waldenstrom macroglobulinemia: IV: *R-CHOP regimen:*** 50 mg/m<sup>2</sup> on day 1 every 21 days for 4 to 8 cycles (in combination with cyclophosphamide, vincristine, prednisone, and rituximab) (Buske 2009)

## Dosing: Pediatric

(For additional information [see "Doxorubicin \(conventional\): Pediatric drug information"](#))

Doxorubicin is associated with a moderate to high emetic potential (depending on dose or regimen); antiemetics are recommended to prevent nausea and vomiting (Dupuis 2011).

**Manufacturer's labeling: Note:** Lower dosages should be considered for patients with inadequate marrow reserve (due to advanced age, prior treatment, or neoplastic marrow infiltration). Cumulative doses above 550 mg/m<sup>2</sup> are associated with an increased risk of cardiomyopathy.

**Metastatic solid tumors, leukemia, or lymphoma: Children and Adolescents: IV:**

Single-agent therapy: 60 to 75 mg/m<sup>2</sup> every 21 days

Combination therapy: 40 to 75 mg/m<sup>2</sup> every 21 to 28 days

**Indication-specific dosing (off-label dosing):**

**Acute lymphoblastic leukemia: IV:**

*DFCI Consortium Protocol 00-01:* Children ≥1 year and Adolescents:

Induction: 30 mg/m<sup>2</sup>/dose on days 0 and 1 of a 4-week cycle (Vrooman 2013)

CNS therapy: High-risk patients: 30 mg/m<sup>2</sup> on day 1 of a 3-week cycle (with dexrazoxane) (Vrooman 2013)

Intensification: High-risk patients: 30 mg/m<sup>2</sup> on day 1 of every 3-week cycle (with dexrazoxane; cumulative doxorubicin dose: 300 mg/m<sup>2</sup>) (Vrooman 2013)

**Ewing sarcoma: Children and Adolescents: IV:**

*VAC/IE regimen:* 75 mg/m<sup>2</sup> on day 1 every 21 days for 5 cycles (in combination with vincristine and cyclophosphamide; after 5 cycles, dactinomycin replaced doxorubicin), alternating cycles with ifosfamide and etoposide for a total of 17 cycles (Grier 2003)

*VAIA regimen:* 30 mg/m<sup>2</sup>/day on days 1 and 2 every 21 days (doxorubicin alternates with dactinomycin; in combination with vincristine and ifosfamide) for 14 cycles (Paulussen 2008)

*VIDE regimen:* 20 mg/m<sup>2</sup>/day over 4 hours on days 1 to 3 every 21 days for 6 cycles (in combination with vincristine, ifosfamide, and etoposide) (Juergens 2006)

**Osteosarcoma: Children and Adolescents: IV:**

*Cisplatin/doxorubicin regimen:* 25 mg/m<sup>2</sup> (bolus infusion) on days 1 to 3 every 21 days (in combination with cisplatin) (Bramwell, 1992)

*High-dose methotrexate/cisplatin/doxorubicin/ifosfamide regimen:*

Preoperative: 75 mg/m<sup>2</sup> administered as a continuous infusion over 24 hours on day 3 of weeks 1 and 7 (in combination with methotrexate, cisplatin, and ifosfamide) (Bacci 2003)

Postoperative: 90 mg/m<sup>2</sup> administered as a continuous infusion over 24 hours on weeks 13, 22, and 31 (in combination with methotrexate, cisplatin, and ifosfamide) (Bacci 2003)

*High-dose methotrexate/cisplatin/doxorubicin regimen:*

Preoperative: 60 mg/m<sup>2</sup> over 8 hours on days 9 and 36 (in combination with methotrexate and cisplatin) (Bacci 2000)

Postoperative: 45 mg/m<sup>2</sup>/day over 4 hours for 2 consecutive days (in combination with methotrexate, cisplatin +/- ifosfamide, +/- etoposide; refer to protocol for criteria, frequency, and other specific information) (Bacci 2000)

**Rhabdomyosarcoma: Children and Adolescents: IV:**

*VAC/IE regimen:* 37.5 mg/m<sup>2</sup> on days 1 and 2 (administered over 18 hours each day) every 6 weeks (in combination with vincristine and cyclophosphamide), alternating cycles with ifosfamide and etoposide (Arndt, 1998)

**Dosing: Geriatric** Refer to adult dosing.

**Dosing: Renal Impairment**

Mild, moderate, or severe impairment: No dosage adjustment provided in the manufacturers' labeling; however, adjustments are likely not necessary given limited renal excretion.

The following adjustments have also been recommended:

CrCl <50 mL/minute: No dosage adjustment necessary (Aronoff 2007).

Hemodialysis: Supplemental dose is not necessary (Aronoff 2007).

Renal insufficiency or hemodialysis: While the AUC of doxorubicin and doxorubicinol (active metabolite) are higher in patients with renal insufficiency, the half-lives are similar to those in

patients without renal impairment. Dosage adjustment does not appear necessary in renal insufficiency or in patients on hemodialysis; administer after dialysis or on a non-dialysis day (Janus 2010).

International Myeloma Working Group Recommendations: The International Myeloma Working Group (IMWG) recommendations suggest that doxorubicin may be administered without dosage adjustment in multiple myeloma patients with renal impairment, including those on dialysis. The IMWG recommends the use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (preferred) or the Modification of Diet in Renal Disease (MDRD) formula to evaluate renal function estimation in multiple myeloma patients with a stable serum creatinine (Dimopoulos 2016).

## Dosing: Hepatic Impairment

The manufacturers' labeling recommends the following adjustments:

Serum bilirubin 1.2 to 3 mg/dL: Administer 50% of dose.

Serum bilirubin 3.1 to 5 mg/dL: Administer 25% of dose.

Severe hepatic impairment (Child-Pugh class C or bilirubin >5 mg/dL): Use is contraindicated.

The following adjustments have also been recommended (Floyd 2006):

Transaminases 2 to 3 times ULN: Administer 75% of dose.

Transaminases >3 times ULN: Administer 50% of dose.

## Dosing: Obesity

*ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer:*

Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs 2012).

**Dosing: Adjustment for Toxicity** Cardiotoxicity: Discontinue in patients who develop signs/symptoms of cardiomyopathy.

**Dosage Forms** Excipient information presented when available (limited, particularly for generics); consult specific product labeling. [DSC] = Discontinued product

Solution, Intravenous, as hydrochloride:

Adriamycin: 2 mg/mL (5 mL, 10 mL, 25 mL, 100 mL)

Generic: 2 mg/mL (5 mL, 10 mL, 25 mL, 100 mL)

Solution, Intravenous, as hydrochloride [preservative free]:

Generic: 2 mg/mL (5 mL, 10 mL, 25 mL, 75 mL, 100 mL)

Solution Reconstituted, Intravenous, as hydrochloride:

Adriamycin: 10 mg (1 ea); 20 mg (1 ea); 50 mg (1 ea)

Generic: 50 mg (1 ea)

Solution Reconstituted, Intravenous, as hydrochloride [preservative free]:

Generic: 10 mg (1 ea); 50 mg (1 ea [DSC])

## Generic Equivalent Available (US) Yes

**Administration** Doxorubicin is associated with a moderate to high emetic potential (depending on dose or regimen); antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Dupuis 2011; Roila 2016).

Administer IV push over at least 3 to 10 minutes or by continuous infusion (infusion via central venous line recommended). Do not administer IM or SubQ. Rate of administration varies by protocol, refer to individual protocol for details. Protect from light until completion of infusion. Avoid contact with alkaline solutions. Monitor for local erythematous streaking along vein and/or facial flushing (may indicate rapid infusion rate); decrease the rate if occurs.

Vesicant; ensure proper needle or catheter placement prior to and during infusion; avoid extravasation.

**Extravasation management:** If extravasation occurs, stop infusion immediately and disconnect (leave cannula/needle in place); gently aspirate extravasated solution (do **NOT** flush the line); remove needle/cannula; elevate extremity. Initiate antidote (dexrazoxane or dimethyl sulfate [DMSO]). Apply dry cold compresses for 20 minutes 4 times daily for 1 to 2 days (Perez Fidalgo 2012); withhold cooling beginning 15 minutes before dexrazoxane infusion; continue withholding cooling until 15 minutes after infusion is completed. Topical DMSO should not be administered in combination with dexrazoxane; may lessen dexrazoxane efficacy.

*Dexrazoxane:* Adults: 1000 mg/m<sup>2</sup> (maximum dose: 2000 mg) IV (administer in a large vein remote from site of extravasation) over 1 to 2 hours days 1 and 2, then 500 mg/m<sup>2</sup> (maximum dose: 1000 mg) IV over 1 to 2 hours day 3; begin within 6 hours of extravasation. Day 2 and day 3 doses should be administered at approximately the same time ( $\pm$  3 hours) as the dose on day 1 (Mouridsen 2007; Perez Fidalgo 2012). **Note:** Reduce dexrazoxane dose by 50% in patients with moderate to severe renal impairment (CrCl <40 mL/minute).

*DMSO:* Children and Adults: Apply topically to a region covering twice the affected area every 8 hours for 7 days; begin within 10 minutes of extravasation; do not cover with a dressing (Perez Fidalgo 2012).

## Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological



safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving, a gown, and (if dosage form allows) CSTDs are required during administration (NIOSH 2016).

## Use

**Breast cancer:** Treatment component of adjuvant therapy in women with evidence of axillary lymph node involvement following resection of primary breast cancer

**Metastatic cancers or disseminated neoplastic conditions:** Treatment of acute lymphoblastic leukemia, acute myeloid leukemia, Wilms tumor, neuroblastoma, soft tissue and bone sarcomas, breast cancer, ovarian cancer, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin lymphoma, non-Hodgkin lymphoma, and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared with other cell types

## Use: Off-Label

Multiple myeloma; Endometrial carcinoma; Uterine sarcoma; Thymomas and thymic malignancies; Waldenström macroglobulinemia; Head and neck cancer; Kidney cancer; Liver cancer

## Medication Safety Issues

### Sound-alike/look-alike issues:

Conventional formulation (Adriamycin) may be confused with the liposomal formulation (Doxil)

DOXOrubicin may be confused with DACTINomycin, DAUNOrubicin, DAUNOrubicin liposomal, doxapram, doxazosin, DOXOrubicin liposomal, epiRUBicin, IDArubicin, valrubicin

Adriamycin may be confused with achromycin, Aredia, Idamycin

### High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

### Administration issues:

Use caution when selecting product for preparation and dispensing; indications, dosages, rate of administration, and adverse event profiles differ between conventional DOXOrubicin hydrochloride solution and DOXOrubicin liposomal. Both formulations are the same concentration. As a result, serious errors have occurred.

### Other safety concerns:

ADR is an error-prone abbreviation

## International issues:

Rubex, a discontinued brand name for DOXOrubicin in the U.S, is a brand name for ascorbic acid in Ireland

## Adverse Reactions

 Frequency not always defined.

### Cardiovascular:

Acute cardiotoxicity: Atrioventricular block, bradycardia, bundle branch block, ECG abnormality, extrasystoles (atrial or ventricular), nonspecific ST or T wave changes on ECG, sinus tachycardia, supraventricular tachycardia, tachyarrhythmia, ventricular tachycardia

Delayed cardiotoxicity: Cardiac failure (manifestations include ascites, cardiomegaly, dyspnea, edema, gallop rhythm, hepatomegaly, oliguria, pleural effusion, pulmonary edema, tachycardia), decreased left ventricular ejection fraction, myocarditis, pericarditis

Central nervous system: Malaise

Dermatologic: Alopecia, discoloration of sweat, pruritus, skin photosensitivity, skin rash; urticaria

Endocrine & metabolic: Amenorrhea, dehydration, hyperuricemia

Gastrointestinal: Abdominal pain, anorexia, diarrhea, discoloration of saliva, gastrointestinal ulcer, mucositis, nausea, vomiting

Genitourinary: Urine discoloration, infertility (may be temporary)

Hematologic & oncologic: Leukopenia ( $\leq 75\%$ ; nadir: 10 to 14 days; recovery: by day 21), neutropenia ( $\leq 75\%$ ; nadir: 10 to 14 days; recovery: by day 21), anemia, thrombocytopenia

Local: Post-injection flare

Neuromuscular & skeletal: Weakness

Ophthalmic: Discoloration of tears

Miscellaneous: Necrosis (colon), radiation recall phenomenon

<1%, postmarketing, and/or case reports: Acute myelocytic leukemia (secondary), anaphylaxis, azoospermia, chills, coma (when in combination with cisplatin or vincristine), conjunctivitis, febrile neutropenia, fever, gonadal disease (gonadal impairment; children), growth suppression (prepubertal), hepatitis, hyperpigmentation (nail, oral mucosa, skin), hypersensitivity reaction (systemic; including angioedema, dysphagia, and dyspnea, pruritus, urticaria), increased serum bilirubin, increased serum transaminases, infection, keratitis, lacrimation, myelodysplastic syndrome, oligospermia, onycholysis, peripheral neurotoxicity (with intra-arterial doxorubicin), phlebosclerosis, pneumonitis (radiation recall; children), seizure (when in combination with cisplatin or vincristine), sepsis, shock, Stevens-Johnson syndrome, toxic epidermal necrolysis, typhlitis (neutropenic)

**Contraindications** Hypersensitivity (including anaphylaxis) to doxorubicin, any component of the formulation, or to other anthracyclines or anthracenediones; recent MI (within past 4 to 6 weeks), severe myocardial insufficiency, severe arrhythmia; previous therapy with high cumulative doses of doxorubicin, daunorubicin, idarubicin, or other anthracycline and anthracenediones; severe persistent drug-induced

myelosuppression or baseline neutrophil count  $<1500/\text{mm}^3$ ; severe hepatic impairment (Child-Pugh class C or bilirubin  $>5 \text{ mg/dL}$ )

## Warnings/Precautions

### *Concerns related to adverse effects:*

- Bone marrow suppression: **[US Boxed Warning]: May cause severe myelosuppression, which may result in serious infection, septic shock, transfusion requirements, hospitalization, and death.** Myelosuppression may be dose-limiting and primarily manifests as leukopenia and neutropenia; anemia and thrombocytopenia may also occur. The nadir typically occurs 10 to 14 days after administration with cell count recovery around day 21. Monitor blood counts at baseline and regularly during therapy.
- Cardiotoxicity: **[US Boxed Warning]: May cause cumulative, dose-related, myocardial toxicity (early or delayed, including acute left ventricular failure and HF). The risk of cardiomyopathy increases with cumulative exposure and with concomitant cardiotoxic therapy; the incidence of irreversible myocardial toxicity increases as the total cumulative (lifetime) dosages approach 300 to 500 mg/m<sup>2</sup> (with an every-3-week regimen). Assess left ventricular ejection fraction (LVEF) with either an echocardiogram or MUGA scan before, during, and after therapy; increase the frequency of assessments as the cumulative dose exceeds 300 mg/m<sup>2</sup>.** Cardiotoxicity is dose-limiting. Delayed cardiotoxicity may occur late in treatment or within months to years after completion of therapy, and is typically manifested by LVEF reduction and/or heart failure (may be life threatening). Subacute effects such as pericarditis and myocarditis may also occur. Early toxicity may consist of tachyarrhythmias, including sinus tachycardia, premature ventricular contractions, and ventricular tachycardia, as well as bradycardia. Electrocardiographic changes including ST-T wave changes, atrioventricular and bundle-branch block have also been reported. These effects are not necessarily predictive of subsequent delayed cardiotoxicity. Total cumulative dose should take into account prior treatment with other anthracyclines or anthracenediones, previous or concomitant treatment with other cardiotoxic agents or irradiation of chest. The risk for delayed cardiotoxicity is estimated to range from 1% to 2% at cumulative lifetime doses of 300 mg/m<sup>2</sup> to 6% to 20% at cumulative lifetime doses of 500 mg/m<sup>2</sup> administered every 3 weeks. Although the risk increases with cumulative dose, irreversible cardiotoxicity may occur at any dose level. Patients with active or dormant cardiovascular disease, concurrent administration of cardiotoxic drugs, prior therapy with other anthracyclines or anthracenediones, prior or concurrent chest irradiation, advanced age, and infants and children are at increased risk. Alternative administration schedules (weekly or continuous infusions) are associated with less cardiotoxicity. Children are at increased risk for developing delayed cardiotoxicity.
- Extravasation: **[US Boxed Warning]: Vesicant; if extravasation occurs, severe local tissue damage leading to tissue injury, blistering, ulceration, and necrosis may occur. Discontinue infusion immediately and apply ice to the affected area. For IV administration only. Do not administer IM or SubQ.** Ensure proper needle or catheter placement prior to and during infusion. Avoid extravasation.
- Fertility impairment: In men, doxorubicin may damage spermatozoa and testicular tissue, resulting in possible genetic fetal abnormalities; may also result in oligospermia, azoospermia, and permanent loss of fertility (sperm counts have been reported to return to normal levels in some men, occurring several years after the end of therapy). In females of reproductive potential, doxorubicin may cause infertility and result in amenorrhea; premature menopause can occur.

- Gastrointestinal toxicity: Doxorubicin is associated with a moderate or high emetic potential (depending on dose or regimen); antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Dupuis 2011; Roila 2016).
- Secondary malignancy: **[US Boxed Warnings]: Secondary acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) have been reported following treatment.** AML and MDS typically occur within 1 to 3 years of treatment; risk factors for development of secondary AML or MDS include treatment with anthracyclines in combination with DNA-damaging antineoplastics (eg, alkylating agents) and/or radiation therapy, heavily pretreated patients, and escalated anthracycline doses.
- Tumor lysis syndrome: May cause tumor lysis syndrome and hyperuricemia (in patients with rapidly growing tumors). Urinary alkalinization and prophylaxis with an antihyperuricemic agent may be necessary. Monitor electrolytes, renal function, and hydration status.

#### ***Disease-related concerns:***

- Hepatic impairment: **[US Boxed Warning]: Dosage modification is recommended in patients with hepatic impairment;** toxicities may be increased in patients with hepatic impairment. Use is contraindicated in patients with severe impairment (Child-Pugh class C or bilirubin >5 mg/dL). Monitor hepatic function tests (eg, transaminases, alkaline phosphatase, and bilirubin) closely.

#### ***Concurrent drug therapy issues:***

- Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

#### ***Special populations:***

- Pediatric: Children are at increased risk for developing delayed cardiotoxicity; long-term periodic cardiac function monitoring is recommended. Doxorubicin may contribute to prepubertal growth failure in children; may also contribute to gonadal impairment (usually temporary). Radiation recall pneumonitis has been reported in children receiving concomitant dactinomycin and doxorubicin.
- Radiation recipients: Use with caution in patients who have received radiation therapy; radiation recall may occur. May increase radiation-induced toxicity to the myocardium, mucosa, skin, and liver.

#### ***Dosage form specific issues:***

- Formulations (conventional vs liposomal): Use caution when selecting product for preparation and dispensing; indications, dosages and adverse event profiles differ between conventional doxorubicin hydrochloride solution and doxorubicin liposomal. Both formulations are the same concentration. As a result, serious errors have occurred.

#### ***Other warnings/precautions:***

- Experienced physician: **[US Boxed Warning]: Should be administered under the supervision of an experienced cancer chemotherapy physician.**
- Vaccines: Administration of live vaccines to immunosuppressed patients may be hazardous.

## **Metabolism/Transport Effects** Substrate of CYP2D6 (major), CYP3A4 (major), P-glycoprotein;

**Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

## **Drug Interactions**

(For additional information: [Launch drug interactions program](#)) Lexicomp®

Abiraterone Acetate: May increase the serum concentration of CYP2D6 Substrates. Management: Avoid concurrent use of abiraterone with CYP2D6 substrates that have a narrow therapeutic index whenever possible. When concurrent use is not avoidable, monitor patients closely for signs/symptoms of toxicity. *Risk D: Consider therapy modification*

Ado-Trastuzumab Emtansine: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline, Systemic). Management: When possible, patients treated with ado-trastuzumab emtansine should avoid anthracycline-based therapy for up to 7 months after stopping ado-trastuzumab emtansine. Monitor closely for cardiac dysfunction in patients receiving this combination. *Risk D: Consider therapy modification*

Ajmaline: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Asunaprevir: May increase the serum concentration of CYP2D6 Substrates. *Risk D: Consider therapy modification*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Bevacizumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline, Systemic). *Risk C: Monitor therapy*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Cardiac Glycosides: May diminish the cardiotoxic effect of Antineoplastic Agents (Anthracycline, Systemic). Antineoplastic Agents (Anthracycline, Systemic) may decrease the serum concentration of Cardiac Glycosides. The effects of liposomal formulations may be unique from those of the free drug, as liposomal formulation have unique drug disposition and toxicity profiles, and liposomes themselves may alter digoxin absorption/distribution. *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Cyclophosphamide: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline, Systemic). *Risk C: Monitor therapy*

CycloSPORINE (Systemic): May increase the serum concentration of DOXOrubicin (Conventional). Management: Consider a doxorubicin dose reduction, as clinically appropriate, when used with

cyclosporine. Use this combination with caution; increase monitoring for toxic effects of doxorubicin. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Moderate): May increase the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to moderate CYP2D6 inhibitors in patients treated with doxorubicin whenever possible. One U.S. manufacturer (Pfizer Inc.) recommends that these combinations be avoided. *Risk D: Consider therapy modification*

CYP2D6 Inhibitors (Strong): May increase the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to strong CYP2D6 inhibitors in patients treated with doxorubicin whenever possible. One U.S. manufacturer (Pfizer Inc.) recommends that these combinations be avoided. *Risk D: Consider therapy modification*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to strong CYP3A4 inducers in patients treated with doxorubicin. One U.S. manufacturer (Pfizer Inc.) recommends that these combinations be avoided. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May increase the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to moderate CYP3A4 inhibitors in patients treated with doxorubicin whenever possible. One U.S. manufacturer (Pfizer Inc.) recommends that these combinations be avoided. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Strong): May increase the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to strong CYP3A4 inhibitors in patients treated with doxorubicin whenever possible. One U.S. manufacturer (Pfizer Inc.) recommends that these combinations be avoided. *Risk D: Consider therapy modification*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dexrazoxane: May diminish the therapeutic effect of DOXOrubicin (Conventional). Management: Do not administer dexrazoxane for cardioprotection at the time of doxorubicin initiation. This recommendation does not apply to the use of dexrazoxane for other indications (e.g., extravasation), or to the use of dexrazoxane later in treatment. *Risk D: Consider therapy modification*

Dipyrrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Enzalutamide: May decrease the serum concentration of CYP3A4 Substrates. Management: Concurrent use of enzalutamide with CYP3A4 substrates that have a narrow therapeutic index should be avoided. Use of enzalutamide and any other CYP3A4 substrate should be performed with caution and close monitoring. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. *Risk D: Consider therapy modification*

Lumefantrine: May increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

Mercaptopurine: DOXOrubicin (Conventional) may enhance the hepatotoxic effect of Mercaptopurine. *Risk C: Monitor therapy*

MiFEPRIStone: May increase the serum concentration of CYP3A4 Substrates. Management: Minimize doses of CYP3A4 substrates, and monitor for increased concentrations/toxicity, during and 2 weeks following treatment with mifepristone. Avoid cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus. *Risk D: Consider therapy modification*

Mitotane: May decrease the serum concentration of CYP3A4 Substrates. Management: Doses of CYP3A4 substrates may need to be adjusted substantially when used in patients being treated with mitotane. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

Panobinostat: May increase the serum concentration of CYP2D6 Substrates. Management: Avoid concurrent use of sensitive CYP2D6 substrates when possible, particularly those substrates with a narrow therapeutic index. *Risk D: Consider therapy modification*

Peginterferon Alfa-2b: May decrease the serum concentration of CYP2D6 Substrates. Peginterferon Alfa-2b may increase the serum concentration of CYP2D6 Substrates. *Risk C: Monitor therapy*

P-glycoprotein/ABCB1 Inducers: May decrease the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to P-glycoprotein inducers in patients treated with doxorubicin whenever possible. One U.S. manufacturer (Pfizer Inc.) recommends that these combinations be avoided. *Risk D: Consider therapy modification*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to P-glycoprotein inhibitors in patients treated with doxorubicin whenever possible. One U.S. manufacturer (Pfizer Inc.) recommends that these combinations be avoided. *Risk D: Consider therapy modification*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

SORafenib: May increase the serum concentration of DOXOrubicin (Conventional). *Risk C: Monitor therapy*

St John's Wort: May decrease the serum concentration of DOXOrubicin (Conventional). Management: Seek alternatives to St. Johns Wort in patients treated with doxorubicin. One US manufacturer (Pfizer) recommends that this combination be avoided. *Risk D: Consider therapy modification*

Stavudine: DOXOrubicin (Conventional) may diminish the therapeutic effect of Stavudine. *Risk C: Monitor therapy*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*



Taxane Derivatives: May decrease the metabolism of DOXOrubicin (Conventional). Management: Consider using docetaxel instead of paclitaxel as a way to avoid this potential interaction, and monitor closely for toxic effects of doxorubicin. Administer doxorubicin prior to paclitaxel when used concomitantly. **Exceptions:** DOCEtaxel. *Risk D: Consider therapy modification*

Taxane Derivatives: May enhance the adverse/toxic effect of Antineoplastic Agents (Anthracycline, Systemic). Taxane Derivatives may increase the serum concentration of Antineoplastic Agents (Anthracycline, Systemic). Taxane Derivatives may also increase the formation of toxic anthracycline metabolites in heart tissue. *Risk D: Consider therapy modification*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the cardiotoxic effect of Antineoplastic Agents (Anthracycline, Systemic). Management: When possible, patients treated with trastuzumab should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab. Monitor closely for cardiac dysfunction in patients receiving anthracyclines with trastuzumab. *Risk D: Consider therapy modification*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Vinflunine: DOXOrubicin (Conventional) may enhance the adverse/toxic effect of Vinflunine. Specifically, the risk for hematologic toxicities may be increased. *Risk C: Monitor therapy*

Zidovudine: DOXOrubicin (Conventional) may enhance the adverse/toxic effect of Zidovudine. DOXOrubicin (Conventional) may diminish the therapeutic effect of Zidovudine. *Risk D: Consider therapy modification*

## **Pregnancy Risk Factor** D ([show table](#))

**Pregnancy Implications** Adverse events have been observed in animal reproduction studies. Based on the mechanism of action, doxorubicin may cause fetal harm if administered during pregnancy (according to the manufacturer's labeling). Advise patients (females of reproductive potential and males with female partners of reproductive potential) to use effective nonhormonal contraception during and for 6 months following therapy. Limited information is available from a retrospective study of women who received doxorubicin (in combination with cyclophosphamide) during the second or third (prior to week 35) trimester for

the treatment of pregnancy-associated breast cancer (Ring 2005). Some pharmacokinetic properties of doxorubicin may be altered in pregnant women (van Hasselt 2014). The European Society for Medical Oncology (ESMO) has published guidelines for diagnosis, treatment, and follow-up of cancer during pregnancy (Peccatori 2013); the guidelines recommend referral to a facility with expertise in cancer during pregnancy and encourage a multidisciplinary team (obstetrician, neonatologist, oncology team). If chemotherapy is indicated, it should **not** be administered in the first trimester, but may begin in the second trimester. There should be a 3-week time period between the last chemotherapy dose and anticipated delivery, and chemotherapy should not be administered beyond week 33 of gestation.

A pregnancy registry is available for all cancers diagnosed during pregnancy at Cooper Health (877-635-4499).

**Breast-Feeding Considerations** Doxorubicin and its metabolites are excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends a decision be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother.

**Monitoring Parameters** CBC with differential and platelet count; liver function tests (bilirubin, ALT/AST, alkaline phosphatase); serum uric acid, calcium, potassium, phosphate and creatinine; hydration status; cardiac function (baseline, periodic, and followup): ECG, left ventricular ejection fraction (echocardiography [ECHO] or multigated radionuclide angiography [MUGA]); monitor infusion site

**Mechanism of Action** Inhibition of DNA and RNA synthesis by intercalation between DNA base pairs by inhibition of topoisomerase II and by steric obstruction. Doxorubicin intercalates at points of local uncoiling of the double helix. Although the exact mechanism is unclear, it appears that direct binding to DNA (intercalation) and inhibition of DNA repair (topoisomerase II inhibition) result in blockade of DNA and RNA synthesis and fragmentation of DNA. Doxorubicin is also a powerful iron chelator; the iron-doxorubicin complex can bind DNA and cell membranes and produce free radicals that immediately cleave the DNA and cell membranes.

## Pharmacodynamics/Kinetics

Distribution:  $V_d$ : 809 to 1,214 L/m<sup>2</sup>; does not cross the blood-brain barrier

Protein binding, plasma: ~75%

Metabolism: Primarily hepatic to doxorubicinol (active), then to inactive aglycones, conjugated sulfates, and glucuronides

Half-life elimination:

Distribution: ~5 minutes

Terminal: 20 to 48 hours

Male: 54 hours; Female: 35 hours

Excretion: Feces (~40% as unchanged drug); urine (5% to 12% as unchanged drug and metabolites)

Clearance:

Infants and Children <2 years: 813 mL/minute/m<sup>2</sup>

Children and Adolescents >2 years: 1,540 mL/minute/m<sup>2</sup>

Adults: 324 to 809 mL/minutes/m<sup>2</sup> (appears to be higher in men than women)

## Pricing: US

### Solution (Adriamycin Intravenous)

2 mg/mL (5 mL): \$12.00

### Solution (DOXOrubicin HCl Intravenous)

2 mg/mL (5 mL): \$12.00

### Solution (reconstituted) (DOXOrubicin HCl Intravenous)

10 mg (1): \$58.52

50 mg (1): \$292.58

**Disclaimer:** The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

**International Brand Names** A.D. Mycin (JO); A.D.Mycin (TH); AD Mycin (KR); Adorucin (VN); Adriablastina (BG); Adriablastina RD (HR); Adriacin (JP); Adriamycin (AU, CN, DK, GB, IS, NO, NZ, SE); Adriamycin CS (MY, SG); Adriamycin PFS (KR); Adriamycin RDF (KR); Adrib (LK); Adriblastin (AT, CH, IL); Adriblastina (AE, AR, BE, BH, CY, CZ, EG, HU, IT, JO, KW, LB, LK, LU, LV, MX, NL, PK, PL, QA, RO, SA, SK, TR, VE); Adriblastina CS (CO); Adriblastina PFS (EE); Adriblastina RTU (CL); Adriblastina Soluzione Pronta (IT); Adriblastine (FR); AdriCept (DE); Adricin (ID); Adrim (IN, JO, VN); Adrimedac (DE); Adrosal (PH, UA); Axibin (PH); Biorrub (BR); Carcinocin (ID); Colhidrol (AR); Dicladox (AR); DOXO-cell (DE); Doxocris (AR); Doxolem RU (MX); Doxopeg (CO, EC); Doxorbin (AR); Doxorub (BD); Doxoruba (LK); Doxorubicin (IN); Doxorubicin Azupharma (DE); Doxorubicin Bigmar (CH); Doxorubicin Bristol (CH); Doxorubicin Ebewe (CH); Doxorubicin Hexal (DE); Doxorubicin NC (DE); Doxorubicin R.P. (DE); Doxorubicin "Paranova" (DK); Doxorubicina (ES); Doxorubicine Asta (FR); Doxorubicine Dakota (FR); Doxorubin (CH, DK, GB, IN, NL, TH); Doxosol (FI); Doxtie (AR, EC); Farmiblastina (ES); Fauldoso (PT); Flavicina (AR); Leubex (AR); Nagun (AR); Oncodoks (UA); Oncodox (PE); Pallagicin (HU); Quimotus (AR); Rastocin (HR); Ribodoxo (DE); Robol (ET); Roxorin (PY, UY); Rubex (BR); Rubicin (PH); Sandobicin (ID); Sindroxocin (HK, HR, PH, RO, RU); Urokit Doxo-cell (DE); Xorubin (BD)

Use of UpToDate is subject to the [Subscription and License Agreement](#).

## REFERENCES

1. *Adriamycin (doxorubicin) [prescribing information]*. Bedford, OH: Bedford Laboratories; April 2012.
2. Arndt CA, Nascimento AG, Schroeder G, et al. Treatment of intermediate risk rhabdomyosarcoma and undifferentiated sarcoma with alternating cycles of vincristine/doxorubicin/cyclophosphamide and etoposide/ifosfamide. *Eur J Cancer*. 1998; 34(8):1224-1229. [PubMed 9849484]
3. Aronoff GR, Bennett WM, Berns JS, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children*. 5th ed. Philadelphia, PA: American College of Physicians; 2007:99.

4. Assikis V, Buzdar A, Yang Y, et al. A phase III trial of sequential adjuvant chemotherapy for operable breast carcinoma: final analysis with 10-year follow-up. *Cancer*. 2003;97(11):2716-2723. [PubMed [12767083](#)]
5. Bacci G, Briccoli A, Rocca M, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: recent experience at the Rizzoli Institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide. *Ann Oncol*. 2003; 14(7):1126-1134. [PubMed [12853357](#)]
6. Bacci G, Ferrari S, Bertoni F, et al. Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the istituto ortopedico Rizzoli according to the istituto ortopedico Rizzoli/osteosarcoma-2 protocol: an updated report. *J Clin Oncol*. 2000;18(24):4016-4027. [PubMed [11118462](#)]
7. Basch E, Prestrud AA, Hesketh PJ, et al; American Society of Clinical Oncology. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2011;29(31):4189-4198. [PubMed [21947834](#)]
8. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: long-term results. *J Clin Oncol*. 2004;22(14):2835-2841. [PubMed [15199092](#)]
9. Bramwell VH, Burgers M, Sneath R, et al. A comparison of two short intensive adjuvant chemotherapy regimens in operable osteosarcoma of limbs in children and young adults: the first study of the European Osteosarcoma Intergroup. *J Clin Oncol*. 1992;10(10):1579-1591. [PubMed [1403038](#)]
10. Bull JM, Tormey DC, Li SH, et al. A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. *Cancer*. 1978;41(5):1649-1657. [PubMed [348293](#)]
11. Buske C, Hoster E, Dreyling M, et al. The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treatment failure in patients with lymphoplasmacytic lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). *Leukemia*. 2009;23(1):153-161. [PubMed [18818699](#)]
12. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*. 2010; 116(12):2040-2045. [PubMed [20548096](#)]
13. Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. *J Clin Oncol*. 2016;34(13):1544-1557. [PubMed [26976420](#)]
14. Doxorubicin [prescribing information]. New York, NY: Pfizer Labs; October 2013.
15. Dupuis LL, Boodhan S, Holdsworth M, et al; Pediatric Oncology Group of Ontario. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. *Pediatr Blood Cancer*. 2013;60(7):1073-1082. [PubMed [23512831](#)]
16. Dupuis LL, Boodhan S, Sung L, et al; Pediatric Oncology Group of Ontario. Guideline for the classification of the acute emetogenic potential of antineoplastic medication in pediatric cancer patients. *Pediatr Blood Cancer*. 2011;57(2):191-198. [PubMed [21465637](#)]
17. Edmonson JH, Ryan LM, Blum RH, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. *J Clin Oncol*. 1993;11(7):1269-1275. [PubMed [8315424](#)]
18. Elias A, Ryan L, Sulkes A, et al. Response to mesna, doxorubicin, ifosfamide, and dacarbazine in 108 patients with metastatic or unresectable sarcoma and no prior chemotherapy. *J Clin Oncol*. 1989;7(9):1208-1216. [PubMed [8315424](#)]
19. Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. *J Clin Oncol*. 2009;27(27):4548-4554. [PubMed [19704068](#)]
20. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *N Engl J Med*. 2010;363(7):640-652. [PubMed [20818855](#)]
21. Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol*. 1990;8(9):1483-1496. [PubMed [2202791](#)]
22. Floyd J, Mirza I, Sachs B, et al, "Hepatotoxicity of Chemotherapy," *Semin Oncol*, 2006;33(1):50-67. [PubMed [16473644](#)]
23. Floyd JD, Nguyen DT, Lobins RL, et al, "Cardiotoxicity of Cancer Therapy," *J Clin Oncol*, 2005;23(30):7685-96. [PubMed

24. Fornasiero A, Daniele O, Ghiotto C, et al. Chemotherapy for invasive thymoma. A 13-year experience. *Cancer*. 1991;68(1):30-33. [PubMed 2049749]
25. Garcia-Suarez J, Banas H, Arribas I, De Miguel D, Pascual T, Burgaleta C. Dose-adjusted EPOCH plus rituximab is an effective regimen in patients with poor-prognostic untreated diffuse large B-cell lymphoma: results from a prospective observational study. *Br J Haematol*. 2007;136(2):276-285. [PubMed 17233819]
26. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood*. 2008;112(7):2687-2693. [PubMed 18625886]
27. Grier HE, Krailo MD, Tarbell NJ, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med*. 2003;348(8):694-701. [PubMed 12594313]
28. Griggs JJ, Mangu PB, Anderson H, et al. "Appropriate Chemotherapy Dosing For Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline," *J Clin Oncol*. 2012;30(13):1553-1561. [PubMed 22473167]
29. Horning SJ, Hoppe RT, Breslin S, Bartlett NL, Brown BW, Rosenberg SA. Stanford V and radiotherapy for locally extensive and advanced Hodgkin's disease: mature results of a prospective clinical trial. *J Clin Oncol*. 2002;20(3):630-637. [PubMed 11821442]
30. Ishii E, Hara T, Ohkubo K, et al, "Treatment of Childhood Acute Lymphoblastic Leukemia With Intermediate Dose Cytosine Arabinoside and Adriamycin," *Med Pediatr Oncol*, 1986, 14(2):73-7. [PubMed 3458999]
31. Janus N, Thariat J, Boulanger H, Deray G, Launay-Vacher V. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. *Ann Oncol*. 2010;21(7):1395-1403. [PubMed 20118214]
32. Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. *Pediatr Blood Cancer*. 2006;47(1):22-29. [PubMed 16572419]
33. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer*. 2004;101(12): 2788-2801. [PubMed 15481055]
34. King PD and Perry MC, "Hepatotoxicity of Chemotherapy," *Oncologist*, 2001, 6(2):162-76. [PubMed 11306728]
35. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. *Blood*. 1995;85(8):2025-2037. [PubMed 7718875]
36. Lee CK, Barlogie B, Munshi N, et al. DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. *J Clin Oncol*. 2003;21(14):2732-2739. [PubMed 12860952]
37. Loehrer PJ Sr, Kim K, Aisner SC, et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. *J Clin Oncol*. 1994;12(6):1164-1168. [PubMed 8201378]
38. Martin M, Pienkowski T, Mackey J, et al; Breast Cancer International Research Group 001 Investigators. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med*. 2005;352(22):2302-2313. [PubMed 15930421]
39. McKelvey EM, Gottlieb JA, Wilson HE, et al. Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. *Cancer*. 1976;38(4):1484-1493. [PubMed 791473]
40. Morgan C, Tillett T, Braybrooke J, et al, "Management of Uncommon Chemotherapy-Induced Emergencies," *Lancet Oncol*, 2011, 12(8):806-14. [PubMed 21276754]
41. Mouridsen HT, Langer SW, Buter J, et al, "Treatment of Anthracycline Extravasation With Savene (Dexrazoxane): Results From Two Prospective Clinical Multicentre Studies," *Ann Oncol*, 2007, 18(3):546-50. [PubMed 17185744]
42. Ogilvie CM, Crawford EA, Siotcavage RL, et al. Treatment of adult rhabdomyosarcoma. *Am J Clin Oncol*. 2010;33(2):128-131. [PubMed 19770626]
43. Omura GA, Major FJ, Blessing JA, et al. A randomized study of Adriamycin with and without dimethyl triazenoimidazole carboxamide in advanced uterine sarcomas. *Cancer*. 1983;52(4):626-632. [PubMed 6344983]
44. Paulussen M, Craft AW, Lewis I, et al; European Intergroup Cooperative Ewing's Sarcoma Study-92. Results of the



- EICESS-92 study: two randomized trials of Ewing's sarcoma treatment—cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. *J Clin Oncol*. 2008;26(27):4385-93. [PubMed 18802150]
45. Peccatori FA, Azim HA Jr, Orecchia R, et al. Cancer, pregnancy and fertility: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24(Suppl 6):vi160-170. [PubMed 23813932]
  46. Pérez Fidalgo JA, García Fabregat L, Cervantes A, et al, "Management of Chemotherapy Extravasation: ESMO-EONS Clinical Practice Guidelines," *Ann Oncol*, 2012, 23(Suppl 7):167-73. [PubMed 22997449]
  47. Pineda-Roman M, Zangari M, Haessler J, et al. Sustained complete remissions in multiple myeloma linked to bortezomib in total therapy 3: comparison with total therapy 2. *Br J Haematol*. 2008;140(6):625-634. [PubMed 18302711]
  48. Randall ME, Filiaci VL, Muss H, et al; Gynecologic Oncology Group Study. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2006;24(1):36-44. [PubMed 16330675]
  49. Ring AE, Smith IE, Jones A, Shannon C, Galani E, Ellis PA. Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals. *J Clin Oncol*. 2005;23:4192-4197. [PubMed 15961766]
  50. Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann Oncol*. 2016;27(suppl 5):v119-v133. [PubMed 27664248]
  51. Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol*. 1995;13(7):1537-1545. [PubMed 7602342]
  52. Seifert CF, Nesser ME, and Thompson DF, "Dexrazoxane in the Prevention of Doxorubicin-Induced Cardiotoxicity," *Ann Pharmacother*, 1994, 28(9):1063-72. [PubMed 7803884]
  53. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. *J Clin Oncol*. 2012;30(24):2946-2955. [PubMed 22802322]
  54. Speyer JL, Green MD, Kramer E, et al, "Protective Effect of the Bispiperazinedione ICRF-187 Against Doxorubicin-Induced Cardiac Toxicity in Women With Advanced Breast Cancer," *N Engl J Med*, 1988, 319(12):745-52. [PubMed 3137469]
  55. Sutton G, Blessing JA, Malfetano JH. Ifosfamide and doxorubicin in the treatment of advanced leiomyosarcomas of the uterus: a Gynecologic Oncology Group study. *Gynecol Oncol*. 1996;62(2):226-229. [PubMed 8751554]
  56. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer*. 2006;106(7):1569-8150. [PubMed 16502413]
  57. Treon SP, Hunter Z, Barnagan AR. CHOP plus rituximab therapy in Waldenstrom's macroglobulinemia. *Clin Lymphoma*. 2005;5(4):273-277. [PubMed 15794864]
  58. US Department of Health and Human Services; Centers for Disease Control and Prevention; National Institute for Occupational Safety and Health. NIOSH list of antineoplastic and other hazardous drugs in healthcare settings 2016. [http://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list\\_2016-161.pdf](http://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf). Updated September 2016. Accessed October 5, 2016.
  59. van Hasselt JGC, Van Calsteren K, Heyns L, et al. Optimizing anticancer drug treatment in pregnant cancer patients: pharmacokinetic analysis of gestation-induced changes for doxorubicin, epirubicin, docetaxel and paclitaxel. *Ann Oncol*. 2014;25(10):2059-2065. [PubMed 24713311]
  60. Von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol*. 1999;17(2):658-667. [PubMed 10080612]
  61. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study-Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. *J Clin Oncol*. 2013;31(9):1202-1210. [PubMed 23358966]
  62. Wilson WH, Grossbard ML, Pittaluga S, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. *Blood*. 2002;99(8):2685-2693. [PubMed 11929754]
  63. Zalupski M, Metch B, Balcerzak S, et al. Phase III comparison of doxorubicin and dacarbazine given by bolus versus

*infusion in patients with soft-tissue sarcomas: a Southwest Oncology Group study. J Natl Cancer Inst. 1991;83(13):926-932. [PubMed 2067035]*

Topic 9391 Version 203.0