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Pegylated liposomal doxorubicin: Drug information

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(For additional information see "Pegylated liposomal doxorubicin: Patient drug information")

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

ALERT: US Boxed Warning

Myocardial toxicity:

Doxorubicin (liposomal) may cause myocardial damage (including congestive heart failure) as the total cumulative dose of doxorubicin approaches 550 mg/m^2. In a clinical study of 250 patients with advanced cancer who were treated with doxorubicin (liposomal), the risk of cardiotoxicity was 11% when the cumulative anthracycline dose was between 450 and 550 mg/m^2. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. The risk of cardiomyopathy may be increased at lower cumulative doses in patients with prior mediastinal irradiation

Infusion reactions:

Acute infusion-related reactions consisting of, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension occurred in 11% of patients with solid tumors treated with doxorubicin (liposomal). Serious, life-threatening and fatal infusion reactions have been reported.

Brand Names: US

Doxil; Lipodox 50; Lipodox [DSC]

Brand Names: Canada

Caelyx

Pharmacologic Category

Antineoplastic Agent, Anthracycline; Antineoplastic Agent, Topoisomerase II Inhibitor

Dosing: Adult

Liposomal formulations of doxorubicin should NOT be substituted for conventional doxorubicin hydrochloride on a mg-per-mg basis.

AIDS-related Kaposi sarcoma: IV: 20 mg/m^2 once every 21 days until disease progression or unacceptable toxicity

Multiple myeloma: IV: 30 mg/m^2 on day 4 every 21 days (in combination with bortezomib) for 8 cycles or until disease progression or unacceptable toxicity (Orlowski 2007)

Multiple myeloma, newly diagnosed (off-label dosing): IV: 40 mg/m^2 on day 1 every 4 weeks (in combination with vincristine and dexamethasone) for at least 4 cycles (Rifkin 2006).

Ovarian cancer, advanced: IV: 50 mg/m^2 once every 28 days until disease progression or unacceptable toxicity

Ovarian cancer, advanced, recurrent (off- label dosing): IV: 40 mg/m^2 once every 28 days (as a single agent) until disease progression or unacceptable toxicity (Ferrandina 2008; Rose 2001) or 30 mg/m^2 once every 28 days (in combination with carboplatin) for at least 6 cycles (Pujade-Lauraine 2010) or 40 mg/m^2 once every 28 days (in combination with bevacizumab) until disease progression or unacceptable toxicity (Pujade-Lauraine 2014).

Breast cancer, metastatic (off-label use): IV: 50 mg/m^2 every 4 weeks (Keller 2004)

Cutaneous T-cell lymphomas (off-label use): IV: 20 mg/m^2 days 1 and 15 every 4 weeks for 6 cycles (Dummer 2012) **or** 20 mg/m^2 every 4 weeks (Wollina 2003)

Hodgkin lymphoma, salvage treatment (off-label use): IV: GVD regimen: 10 mg/m^2 (post-transplant patients) or 15 mg/m^2 (transplant-naive patients) days 1 and 8 every 3 weeks (in combination with gemcitabine and vinorelbine) for 2 to 6 cycles (Bartlett 2007)

Soft tissue sarcoma, advanced (off-label use): IV: 50 mg/m^2 every 4 weeks for 6 cycles (Judson 2001)

Uterine sarcoma, advanced or recurrent (off-label use): IV: 50 mg/m^2 every 4 weeks until disease progression or unacceptable toxicity (Sutton 2005)

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Dosing: Hepatic Impairment

US labeling: There are no dosage adjustments provided in the manufacturer's labeling. However, doxorubicin is predominantly hepatically eliminated and reduced doxorubicin liposomal doses are recommended in patients with serum bilirubin ≥1.2 mg/dL.

Canadian labeling:

AIDS-related Kaposi sarcoma:

Bilirubin 1.2 to 3 mg/dL: Reduce dose to 50% of normal dose

Bilirubin >3 mg/dL: Reduce dose to 25% of normal dose

Breast cancer and ovarian cancer:

Bilirubin 1.2 to 3 mg/dL: Initial dose: Reduce dose to 75% of normal dose; if tolerated and no change in bilirubin/hepatic enzymes, may increase to full dose with cycle 2

Bilirubin >3 mg/dL: Initial dose: Reduce dose to 50% of normal dose; if tolerated and no change in bilirubin/hepatic enzymes, may increase dose to 75% of normal dose for cycle 2; if cycle 2 dose tolerated, may increase to full dose for subsequent cycles.

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

US labeling: **Note:** Once a dosage reduction due to toxicity has been implemented, the dose should not be increased at a later time.

Hematologic toxicity:

AIDS-related Kaposi sarcoma and ovarian cancer:

Grade 1 (ANC 1,500 to 1,900/mm^3 ***or platelets*** *75,000 to 150,000/mm^3):* No dosage adjustment necessary.

Grade 2 (ANC 1,000 to <1,500/mm^3 ***or platelets*** *50,000 to <75,000/mm^3):* Delay treatment until ANC ≥1,500/mm^3 and platelets ≥75,000/mm^3; resume treatment at previous dose.

Grade 3 (ANC 500 to 999/mm^3 or platelets 25,000 to <50,000/mm^3): Delay treatment until ANC ≥1,500/mm^3 and platelets ≥75,000/mm^3; resume treatment at previous dose.

Grade 4 (ANC <500/mm^3 or platelets <25,000/mm^3): Delay treatment until ANC ≥1,500/mm^3 and platelets ≥75,000/mm^3; then resume at 25% dose reduction or continue at previous dose with granulocyte growth factor support.

Multiple myeloma (in combination with Bortezomib) (see Bortezomib monograph for bortezomib dosage reduction with toxicity guidelines):

Fever ≥38°C and ANC <1,000/mm^3: If prior to doxorubicin liposomal treatment (day 4), do not administer (withhold); if after doxorubicin liposomal administered, reduce dose by 25% in next cycle.

ANC <500/mm^3, platelets <25,000/mm^3, hemoglobin <8 g/dL: If prior to doxorubicin liposomal treatment (day 4); do not administer (withhold); if after doxorubicin liposomal administered and if bortezomib dose reduction occurred for hematologic toxicity, reduce dose by 25% in next cycle

Nonhematologic toxicity:

Hand-foot syndrome (HFS):

Grade 1 (mild erythema, swelling, or desquamation not interfering with daily activities): If no prior grade 3 or 4 HFS toxicity, no dosage adjustment is necessary. If prior grade 3 or 4 HFS toxicity, delay dose up to 2 weeks and decrease dose by 25%.

Grade 2 (erythema, desquamation, or swelling interfering with, but not precluding, normal physical activities; small blisters or ulcerations <2 cm in diameter): Delay dosing up to 2 weeks or until resolved to grade 0 or 1. If after 2 weeks there is no resolution, discontinue liposomal doxorubicin. If resolved to grade 0 or 1 within 2 weeks and no prior grade 3 or 4 HFS, continue treatment at previous dose. If a prior grade 3 or 4 HFS has occurred,

decrease dose by 25%.

Grade 3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing): Delay dosing up to 2 weeks or until resolved to grade 0 or 1, then decrease dose by 25%. If no resolution after 2 weeks, discontinue liposomal doxorubicin.

Grade 4 (diffuse or local process causing infectious complications, or a bedridden state or hospitalization): Delay dosing up to 2 weeks or until resolved to grade 0 or 1, then decrease dose by 25%. If no resolution after 2 weeks, discontinue liposomal doxorubicin.

Infusion reaction: Temporarily stop infusion until resolution and then resume at a reduced rate. For serious or life threatening reaction, discontinue infusion.

Stomatitis:

Grade 1 (painless ulcers, erythema, or mild soreness): If no prior grade 3 or 4 toxicity, no dosage adjustment is necessary. If prior grade 3 or 4 toxicity, delay dose up to 2 weeks and decrease dose by 25%.

Grade 2 (painful erythema, edema, or ulcers, but can eat): Delay dosing up to 2 weeks or until resolved to grade 0 or 1. If after 2 weeks there is no resolution, discontinue liposomal doxorubicin. If resolved to grade 0 or 1 within 2 weeks and no prior grade 3 or 4 stomatitis, continue treatment at previous dose. If prior grade 3 or 4 stomatitis, decrease dose by 25%.

Grade 3 (painful erythema, edema, or ulcers, and cannot eat): Delay dosing up to 2 weeks or until resolved to grade 0 or 1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks there is no resolution, discontinue liposomal doxorubicin.

Grade 4 (requires parenteral or enteral support): Delay dosing up to 2 weeks or until resolved to grade 0 or 1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks there is no resolution, discontinue liposomal doxorubicin.

Multiple myeloma (in combination with Bortezomib) (see Bortezomib monograph for bortezomib dosage reduction with toxicity guidelines):

Grade 3 or 4 nonhematologic toxicity: Delay dose until resolved to grade <2 and then reduce dose by 25%

Neuropathic pain or peripheral neuropathy: No dose reductions needed for doxorubicin liposomal, refer to Bortezomib monograph for bortezomib dosing adjustment.

Canadian labeling:

Hematologic toxicity:

Breast cancer, ovarian cancer: Refer to US dosage adjustment for hematologic toxicity section.

AIDS-related Kaposi sarcoma:

Grade 1 ***or*** *grade 2 (ANC 1,500 to 1,900/mm^3* ***or platelets*** *75,000 to 150,000/mm^3* ***or*** *ANC*

1,000 to <1,500/ mm^3 ***or platelets*** *50,000 to <75,000/mm^3):* No dosage adjustment necessary.

Grade 3 (ANC 500 to 999/mm^3 and platelets 25,000 to <50,000/mm^3): Delay treatment until ANC ≥1,000/mm^3 and/or platelets ≥50,000/mm^3 and then resume with a 25% dose reduction.

Grade 4 (ANC <500/mm^3 and platelets <25,000/mm^3): Delay treatment until ANC ≥1,000/mm^3 and/or platelets ≥50,000/mm^3 and then resume with a 50% dose reduction.

Nonhematologic toxicity:

Breast cancer, ovarian cancer:

Hand-foot syndrome (HFS; palmar-plantar erythrodysesthesia):

Grade 1 (mild erythema, swelling, or desquamation not interfering with daily activities): If at weeks 4 and 5 following prior dose, resume unless patients has experienced prior grade 3 or 4 HFS toxicity (if so, wait an additional week). If at week 6, decrease dose by 25%; return to 4-week interval.

Grade 2 (erythema, desquamation, or swelling interfering with, but not precluding, normal physical activities; small blisters or ulcerations <2 cm in diameter): If at weeks 4 and 5 following prior dose, wait an additional week. If at week 6, decrease dose by 25%; return to 4-week interval.

Grade 3 ***or*** *grade 4 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing* ***or*** *diffuse or local process causing infectious complications, or a bedridden state or hospitalization):* If at weeks 4 and 5 following prior dose, wait an additional week. If at week 6, discontinue therapy.

Stomatitis:

Grade 1 (painless ulcers, erythema, or mild soreness): If at weeks 4 and 5 following prior dose, resume unless patients has experienced prior grade 3 or 4 HFS toxicity (if so, wait an additional week). If at week 6, decrease dose by 25%; return to 4-week interval or discontinue therapy (based on physical assessment).

Grade 2 (painful erythema, edema, or ulcers, but can eat): If at weeks 4 and 5 following prior dose, wait an additional week. If at week 6, decrease dose by 25%; return to 4-week interval or discontinue therapy (based on physical assessment).

Grade 3 ***or*** *grade 4 (painful erythema, edema, or ulcers, and cannot eat or requires parenteral or enteral support):* If at weeks 4 and 5 following prior dose, wait an additional week. If at week 6, discontinue therapy.

Aids-related Kaposi sarcoma:

Hand-foot syndrome (HFS; palmar-plantar erythrodysesthesia):

Grade 0 (no symptoms): If at week 3 or 4 following prior dose, redose at a 2-to 3-week interval.

Grade 1 (mild erythema, swelling, or desquamation not interfering with daily activities): If at

week 3 following prior dose, resume unless patients has experienced prior grade 3 or 4 HFS toxicity (if so, wait an additional week). If at week 4 following prior dose, decrease dose by 25% and return to 3-week interval.

Grade 2 (erythema, desquamation, or swelling interfering with, but not precluding, normal physical activities; small blisters or ulcerations <2 cm in diameter): If at week 3 following prior dose, wait an additional week. If at week 4 following prior dose, decrease dose by 50% and return to 3-week interval.

Grade 3 ***or*** *grade 4 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing, diffuse or local process causing infectious complications, or a bedridden state or hospitalization):* If at week 3 following prior dose, wait an additional week. If at week 4, discontinue therapy.

Stomatitis:

Grade 1 (painless ulcers, erythema, or mild soreness): No dosage adjustment necessary.

Grade 2 (painful erythema, edema, or ulcers, but can eat): Wait 1 week and if symptoms improve, resume at 100% dose.

Grade 3 (painful erythema, edema, or ulcers, and cannot eat): Wait 1 week and if symptoms improve, resume with a 25% dose reduction.

Grade 4 (requires parenteral or enteral support): Wait 1 week and if symptoms improve, resume with a 50% dose reduction.

Dosage Forms

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

Injectable, Intravenous, as hydrochloride:

Doxil: 2 mg/mL (10 mL, 25 mL)

Lipodox: 2 mg/mL (10 mL [DSC])

Lipodox 50: 2 mg/mL (25 mL)

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

Generic Equivalent Available (US)

Yes

Dosage Forms Considerations

Doxil, Lipodox, generic doxorubicin HCl liposomal (Sun Pharma), and Caelyx (Canadian product) are pegalyated liposomal formulations of doxorubicin hydrochloride.

Myocet (Canadian product) is encapsulated liposomes of doxorubicin hydrochloride.

Dosage Forms: Canada

Information with regard to form, strength, and availability of products uniquely available in Canada but currently not available in the US. Refer also to Dosage forms.

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Injection, solution, as hydrochloride, pegylated:

Caelyx: 2 mg/mL (10 mL, 25 mL)

Administration Monitor for infusion reaction. For IV infusion only; do not administer IV push. If contact with skin/mucosa occurs, wash immediately with soap and water.

Administer IVPB over 60 minutes; the manufacturer recommends infusing the first dose at initial rate of 1 mg/minute to minimize risk of infusion reactions; if no infusion-related reactions are observed, then increase the infusion rate for completion over 1 hour. Do **NOT** administer undiluted. Do **NOT** infuse with in-line filters. Do not mix with other medications. Monitor for local erythematous streaking along vein and/or facial flushing (may indicate rapid infusion rate).

For multiple myeloma, administer doxorubicin liposomal after bortezomib on day 4 of each cycle.

Irritant (Perez Fidalgo 2012); monitor infusion site; avoid extravasation. Assure proper needle or catheter position prior to administration.

Extravasation management: If extravasation, infiltration, or burning/stinging sensation 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 (Perez Fidalgo 2012; Polovich 2009). Do not apply pressure to the site. Apply ice to the site for 15 minutes 4 times a day for 3 days.

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

AIDS-related Kaposi sarcoma: Treatment of AIDS-related Kaposi sarcoma (after failure of or intolerance to prior systemic therapy)

Multiple myeloma: Treatment of multiple myeloma (in combination with bortezomib) in patients who are bortezomib-naïve and have received at least 1 prior therapy

Ovarian cancer, advanced: Treatment of progressive or recurrent ovarian cancer (after platinum-based treatment)

Use: Off-Label

Breast cancer, metastatic; Hodgkin lymphoma (salvage treatment); Cutaneous T-cell lymphomas (mycosis fungoides and Sézary syndrome); Soft tissue sarcomas, advanced; Uterine sarcoma, advanced or recurrent

Medication Safety Issues

Sound-alike/look-alike issues:

Liposomal formulation (Doxil) may be confused with the conventional formulation (Adriamycin)

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

Doxil may be confused with Doxy 100, Paxil

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. Liposomal formulation of doxorubicin should NOT be substituted for doxorubicin hydrochloride on a mg-per-mg basis.

International issues:

Caelyx [Canada] may be confused with Myocet [Canada]; product formulations and indications differ

Doxil [US, Israel] may be confused with Doxal brand name for doxepin [Finland] and pyridoxine/thiamine [Brazil]

Adverse Reactions Frequency not always defined.

>10%:

Cardiovascular: Cardiomyopathy (dose related: 11%; Kaposi sarcoma: <1%), cardiotoxicity (11%), chest tightness (11%), flushing (11%), hypotension (1% to 11%)

Central nervous system: Fatigue (>20%), headache (≤11%)

Dermatologic: Palmar-plantar erythrodysesthesia (ovarian cancer: ≤51%; grades 3/4: 24%), skin rash (grades 3/4: 29%, Kaposi sarcoma: 1% to 5%), alopecia (9% to 19%), facial swelling (11%)

Gastrointestinal: Nausea (ovarian cancer: 46%; Kaposi sarcoma: 17% to 18%; grades 3/4: 5%),

stomatitis (grades 3/4: 41%, Kaposi sarcoma: 5% to 8%), vomiting (grades 3/4: 33%; Kaposi sarcoma: 8%), constipation (>20%), diarrhea (grades 3/4: 21%; Kaposi sarcoma: 3% to 8%), anorexia (20%; Kaposi sarcoma: 1% to 5%), mucous membrane disease (14%; grades 3/4: 4%), dyspepsia 12%; grades 3/4: <1%)

Hematologic & oncologic: Thrombocytopenia (dose related, Kaposi sarcoma: 1% to 61%), neutropenia (dose related: 4% to 49%), leukopenia (37%), anemia (16% to 58%; dose related <1% to 5%)

Neuromuscular & skeletal: Weakness (grades 3/4: 40%; Kaposi sarcoma: 7% to 10%), back pain (grades 3/4: 11% to 12%; Kaposi sarcoma: 1% to 5%)

Respiratory: Pharyngitis (16%; Kaposi sarcoma <1%), dyspnea (1% to 15%)

Miscellaneous: Fever (21%; Kaposi sarcoma: 8% to 9%; grades 3/4: <1%), infusion related reaction (7% to 11%)

1% to 10%:

Cardiovascular: Cardiac arrest (≤10%), chest pain (Kaposi sarcoma: 1% to 5%), deep thrombophlebitis (ovarian cancer: 1% to 10%), tachycardia (1% to 10%), vasodilation (ovarian cancer: 1% to 10%)

Central nervous system: Depression (ovarian cancer: 1% to 10%), dizziness (1% to 10%), drowsiness (1% to 10%), chills (Kaposi sarcoma: 1% to 5%)

Dermatologic: Acne vulgaris (ovarian cancer: 1% to 10%), ecchymoses (ovarian cancer: 1% to 10%), exfoliative dermatitis (ovarian cancer: 1% to 10%), fungal dermatitis (ovarian cancer: 1% to 10%), furunculosis (ovarian cancer: 1% to 10%), herpes simplex dermatitis (1% to 10%), pruritus (1% to 10%), skin discoloration (ovarian cancer: 1% to 10%), vesiculobullous dermatitis (ovarian cancer: 1% to 10%), xeroderma (ovarian cancer: 1% to 10%), maculopapular rash (≤10%)

Endocrine & metabolic: Hypercalcemia (ovarian cancer: 1% to 10%), hypokalemia (ovarian cancer: 1% to 10%), hyponatremia (ovarian cancer: 1% to 10%), weight loss (1% to 10%), dehydration (≤10%), hyperglycemia (1% to 5%)

Gastrointestinal: Dysphagia (1% to 10%), esophagitis (ovarian cancer: 1% to 10%), intestinal obstruction (ovarian cancer: 1% to 10%), oral candidiasis (1% to 10%), oral mucosa ulcer (1% to 10%), dysgeusia (1% to ≤10%), abdomen enlarged (ovarian cancer 1% to 5%), glossitis (1% to 5%), cachexia

Genitourinary: Hematuria (ovarian cancer: 1% to 10%), hemorrhagic cystitis, urinary tract infection (ovarian cancer: 1% to 10%), vulvovaginal candidiasis (ovarian cancer 1% to 10%)

Hematologic & oncologic: Rectal hemorrhage (ovarian cancer: 1% to 10%), hemolysis (1% to 5%), prolonged prothrombin time (1% to 5%), bone marrow depression (Kaposi sarcoma), progression of cancer (Kaposi sarcoma)

Hepatic: Hyperbilirubinemia (1% to 10%), increased serum alkaline phosphatase (Kaposi sarcoma 1% to 8%), increased serum ALT (Kaposi sarcoma 1% to 5%)

Hypersensitivity: Hypersensitivity reaction (Kaposi sarcoma 1% to 5%)

Infection: Infection (1% to 12%), herpes zoster (≤10%), paresthesia (5%), myalgia (ovarian cancer:

1% to 5%), neuropathy (ovarian cancer 1% to 5%), toxoplasmosis (Kaposi sarcoma)

Ophthalmic: Dry eye syndrome (ovarian cancer: 1% to 10%), conjunctivitis (≤10%), retinitis (Kaposi sarcoma 1% to 5%) optic neuritis (Kaposi sarcoma)

Respiratory: Epistaxis (ovarian cancer: 1% to 10%), pneumonia (1% to 10%), rhinitis (ovarian cancer: 1% to 10%), sinusitis (ovarian cancer: 1% to 10%), increased cough (≤10%), cough (Kaposi sarcoma)

<1%, postmarketing, and/or case reports (Limited to important or life-threatening): Abnormal vision, abscess, acute brain syndrome, albuminuria, alkaline phosphatase increased anaphylactic reaction, anxiety, arthralgia, asthma, balanitis, blindness, bone pain, bronchitis, bundle branch block (Kaposi sarcoma), BUN increased, candidiasis (Kaposi sarcoma), cardiomegaly, cardiomyopathy, cellulitis, CHF, colitis, confusion, congestive heart failure (Kaposi sarcoma), creatinine increased, cryptococcosis, cryptococcosis (Kaposi sarcoma), diabetes mellitus, dysuria,edema, emotional lability, erythema multiforme, erythema nodosum, eosinophilia, fecal impaction, flatulence, flu-like syndrome, gastritis, hemorrhage, hepatic failure, hepatitis (Kaposi sarcoma), hepatosplenomegaly, hyperkalemia, hyperlipidemia, hypernatremia, hyperuricemia, hyperventilation, hypoglycemia, hypomagnesemia, hypophosphatemia, hypoproteinemia, hypothermia, injection site hemorrhage, injection site pain, insomnia, jaundice, ketosis, lactic dehydrogenase increased, lymphadenopathy, lymphangitis, migraine, myositis, muscle spasm, optic neuritis, pain, pallor, palpitations (Kaposi sarcoma), pancreatitis, pericardial effusion, petechia, pneumothorax, peripheral edema, pleural effusion, pulmonary embolism, radiation injury, sclerosing cholangitis, seizure, secondary acute myelocytic leukemia, sepsis (Kaposi sarcoma), skin necrosis, skin ulcer, syncope, squamous cell carcinoma, Stevens-Johnson syndrome, tenesmus, thrombophlebitis (Kaposi sarcoma), thromboplastin decreased, thrombosis (Kaposi sarcoma), tinnitus, toxic epidermal necrolysis, urticaria, vertigo (Kaposi sarcoma), ventricular arrhythmia (Kaposi sarcoma)

Contraindications

Severe hypersensitivity (including anaphylaxis) to doxorubicin liposomal, conventional doxorubicin, or any component of the formulation

Canadian labeling: Additional contraindications (not in the US labeling): Breast-feeding

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: Neutropenia, anemia, and thrombocytopenia may occur. Monitor blood counts. Treatment delay, dosage modification, or discontinuation may be required. Hematologic toxicity may occur at a higher frequency and severity with combination chemotherapy.

• Infusion reactions: **[US Boxed Warning]: Acute infusion-related reactions consisting of, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension occurred in 11% of patients with solid tumors treated with doxorubicin (liposomal). Serious, life-threatening and fatal infusion reactions have been reported.** Infusion reactions have also included chest pain, pruritus, rash, cyanosis, syncope, tachycardia, bronchospasm, asthma, and apnea. Most reactions occurred during the first infusion. Some reactions have resulted in dose interruption. Medication and

equipment to manage infusion reactions should be immediately available during infusion. Initiate infusion at a rate of 1 mg/minute, with the rate increased (to complete infusion over 60 minutes) as tolerated. If an infusion reaction occurs, temporarily interrupt infusion until resolved and resume at a reduced rate. Discontinue for serious or life-threatening infusion reactions.

• Myocardial toxicity: **[US Boxed Warning]: Doxorubicin liposomal may cause myocardial damage (including congestive heart failure) as the total cumulative dose of doxorubicin approaches 550 mg/m^2. In a clinical study of 250 patients with advanced cancer who were treated with doxorubicin liposomal, the risk of cardiotoxicity was 11% when the cumulative anthracycline dose was between 450 to 550 mg/m^2. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. The risk of cardiomyopathy may be increased at lower cumulative doses in patients with prior mediastinal irradiation.** Myocardial damage may manifest as acute left ventricular failure; cardiotoxicity is defined as a >20% decrease in resting left ventricular ejection fraction (LVEF) from baseline (if LVEF remained in the normal range) or a >10% decrease from baseline (where LVEF was less than the institutional lower limit of normal). Some patients developed signs/symptoms of heart failure without documented evidence of cardiotoxicity. The risk of cardiomyopathy with doxorubicin is generally proportional to the cumulative exposure, although the relationship between cumulative doxorubicin liposomal dose and the risk of cardiotoxicity is not known. Anthracycline-induced cardiotoxicity may be delayed (after discontinuation of anthracycline treatment). Assess left ventricular function with echocardiogram or MUGA prior to and during treatment to detect acute changes; monitor after treatment to detect delayed cardiotoxicity. Use in patients with a history of cardiovascular disease only if potential benefits outweigh cardiovascular risk.

• Palmar-plantar erythrodysesthesia (hand-foot syndrome): Hand-foot syndrome has been reported in patients receiving doxorubicin liposomal. It is usually seen after 2 to 3 treatment cycles, although may also occur earlier. Dosage modification may be required; in severe or debilitating cases, treatment discontinuation may be required.

• Secondary malignancy: Cases of secondary oral cancers (primarily squamous cell carcinoma) have been reported with long-term (>1 year) doxorubicin liposomal exposure; these secondary oral malignancies have occurred during treatment and up to 6 years after treatment. The development of oral ulceration or discomfort should be monitored and further evaluated in patients with past or present use of doxorubicin liposomal. Tissue distribution of the liposomal doxorubicin compared to free doxorubicin may play a role in the development of oral secondary malignancies associated with long-term use.

Disease-related concerns:

• Hepatic impairment: Pharmacokinetics in patients with hepatic impairment have not been adequately studied. Doxorubicin is predominantly eliminated hepatically; reduce doxorubicin liposomal dose in patients with serum bilirubin ≥1.2 mg/dL.

Special populations:

• Splenectomized patients: Use in splenectomized patients with AIDS-related Kaposi sarcoma has not been studied and is not recommended (Canadian labeling [Caelyx] 2016).

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.

Dosage form specific issues:

• Liposomal vs conventional formulation dosing: Liposomal formulations of doxorubicin should **NOT** be substituted for conventional doxorubicin hydrochloride on a mg-per-mg basis.

Metabolism/Transport Effects

Substrate of CYP2D6 (major), CYP3A4 (major); **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*

Aprepitant: May increase the serum concentration of CYP3A4 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*

CYP2D6 Inhibitors (Moderate): May decrease the metabolism of CYP2D6 Substrates. *Risk C: Monitor therapy*

CYP2D6 Inhibitors (Strong): May decrease the metabolism of CYP2D6 Substrates. *Risk D: Consider therapy modification*

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

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. *Risk D: Consider therapy modification*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. *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*

Dipyrone: 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*

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

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*

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*

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

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*

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*

QuiNINE: May increase the serum concentration of CYP2D6 Substrates. *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*

Simeprevir: May increase 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*

St John's Wort: May decrease the serum concentration of CYP3A4 Substrates. Management: Consider an alternative for one of the interacting drugs. Some combinations may be specifically contraindicated. Consult appropriate manufacturer labeling. *Risk D: Consider therapy modification*

Stavudine: DOXOrubicin (Liposomal) 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 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 (Liposomal) may enhance the adverse/toxic effect of Vinflunine. Specifically, the risk for hematologic toxicities may be increased. DOXOrubicin (Liposomal) may increase the serum concentration of Vinflunine. Vinflunine may decrease the serum concentration of DOXOrubicin (Liposomal). *Risk C: Monitor therapy*

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

Pregnancy Implications Adverse events were observed in animal reproduction studies. May cause fetal harm if administered during pregnancy. Women and men of reproductive potential should use effective contraception during therapy and for 6 months after treatment. Doxorubicin liposomal may damage spermatozoa and testicular tissue in males and may result in oligospermia, azoospermia, and permanent loss of fertility. May cause amenorrhea, infertility, and premature menopause in females.

Breast-Feeding Considerations It is not known if doxorubicin liposomal is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding should be discontinued during treatment.

Monitoring Parameters CBC with differential and platelet count, liver function tests (ALT/AST, bilirubin, alkaline phosphatase); monitor infusion site, monitor for infusion reactions, hand-foot syndrome, stomatitis, and oral ulceration/discomfort suggestive of secondary oral malignancy

Cardiac function (left ventricular ejection fraction [LVEF]; baseline and periodic); echocardiography, or MUGA scan may be used.

Mechanism of Action Doxorubicin inhibits DNA and RNA synthesis by intercalating between DNA base pairs causing steric obstruction and inhibits topoisomerase-II at the point of DNA cleavage. Doxorubicin is also a powerful iron chelator. The iron-doxorubicin complex can bind DNA and cell membranes, producing free hydroxyl (OH) radicals that cleave DNA and cell membranes. Active throughout entire cell cycle. Doxorubicin liposomal is a pegylated formulation which protects the liposomes, and thereby increases blood circulation time.

Pharmacodynamics/Kinetics

Distribution: V_{dss}: ~2.7 to 2.8 L/m^2; largely confined to vascular fluid

Protein binding, plasma: Unknown; nonliposomal (conventional) doxorubicin: ~70%

Half-life elimination: Terminal: Distribution: ~4.7 to 5.2 hours, Elimination: ~52 to 55 hours

Metabolism: Hepatic and in plasma to doxorubicinol and the sulfate and glucuronide conjugates of 4-demethyl,7-deoxyaglycones

Pricing: US

Injection (Doxil Intravenous)

2 mg/mL (10 mL): $1293.48

Injection (DOXOrubicin HCl Liposomal Intravenous)

2 mg/mL (10 mL): $1162.80

Injection (Lipodox 50 Intravenous)

2 mg/mL (25 mL): $2878.00

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

Caelyx (AE, AR, AT, AU, BE, BH, BR, CH, CL, CN, CO, CR, CY, CZ, DE, DK, DO, EC, EE, ES, FI, FR, GB, GR, GT, HK, HN, HR, HU, ID, IE, IL, IN, IS, IT, JO, KR, LB, LT, LU, LV, MT, MX, MY, NI, NL, NO, NZ, PA, PE, PH, PL, PT, QA, RO, RU, SE, SG, SI, SK, SV, TH, TR, TW, UY, VE, VN); Doxil (IL); Doxopeg (AR, BR, CL, MX, PE); Lipo-Dox (TH, TW); Myocet (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IL, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SK, TR); Zuclodox-DRS (CR, DO, GT, HN, NI, PA, SV)

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