

POLICY NUMBER UM_1235	SUBJECT Doxil/Lipodox™ (liposomal doxorubicin)		DEPT/PROGRAM Utilization Management	PAGE 1 OF 7
DATE REVIEWED 12/12/12, 12/10/13, 3/16/15, 5/19/16	APPROVAL DATE 5/24/16	EFFECTIVE DATE 5/24/16	REVISION DATES (latest version listed last) 12/12/12, 12/11/13, 3/16/15, 3/27/15, 5/24/16	
PRIMARY BUSINESS OWNER: UM APPROVED BY: Dr. Andrew Hertler		COMMITTEE/BOARD APPROVAL Utilization Management Committee		
URAC STANDARDS		ADDITIONAL AREAS OF IMPACT		
CMS REQUIREMENTS	STATE/FEDERAL REQUIREMENTS		APPLICABLE LINES OF BUSINESS Oncology	

I. PURPOSE

To define and describe the accepted indications for Doxil/Lipodox (liposomal doxorubicin) usage in the treatment of cancer

II. DEFINITIONS

Doxil/Lipodox (liposomal doxorubicin): Doxorubicin is an anthracycline topoisomerase inhibitor isolated from *Streptomyces peucetius* var. *caesius*. Doxorubicin is the active cytotoxic agent in Doxorubicin Liposomal. The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

Doxil/Lipodox (liposomal doxorubicin) is FDA approved for the treatment of:

- AIDS-related Kaposi's sarcoma, In patients that have progressed or are intolerant to other combination chemotherapy regimens
- Multiple myeloma, In combination with bortezomib in patients who have not received bortezomib and have received at least one prior therapy
- Ovarian carcinoma, In patients whose disease has progressed or recurred after platinum-based chemotherapy

Non-FDA approved indications include:

- Breast Cancer
- Endometrial Cancer
- Hodgkin Lymphoma
- Non-Hodgkin's Lymphoma
- Soft Tissue Sarcoma

Doxil/Lipodox (liposomal doxorubicin) is available in 20 mg and 50 mg vials at a concentration of 2mg/mL.

III. POLICY

New Century is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century may be deemed as not approvable and therefore not reimbursable.

Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must be supported by, at minimum, two peer reviewed citations. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: Doxil/Lipodox (liposomal doxorubicin) may be considered medically necessary when any of the following selection criteria is met:

1. **Aids related Kaposi's Sarcoma (KS)**
 - a. For the treatment of HIV-related Kaposi's sarcoma in members with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to other therapy.
2. **Multiple Myeloma**
 - a. For the treatment of relapsed or refractory multiple myeloma and Doxil/Lipodox (liposomal doxorubicin) is being used in combination with bortezomib in patients who have received at least 1 prior therapy and is bortezomib naive.
3. **Ovarian cancer**
 - a. Doxil/Lipodox (liposomal doxorubicin) is being used for the treatment of ovarian cancer that has progressed or recurred for the **ONE** of the following:
 - i. After platinum-based chemotherapy as a single agent or in combination with bevacizumab if bevacizumab not previously received .
 - ii. If platinum sensitive, in combination with carboplatin for persistent disease or recurrence.
4. **Breast cancer**
 - a. Preferred single agent for patients with recurrent or metastatic disease that is
 - i. hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative with visceral crisis
 - ii. HER2-negative and either hormone receptor-negative or hormone receptor-positive and endocrine therapy refractory
 - iii. progressive with no clinical benefit after three consecutive endocrine therapy regimens or with symptomatic visceral disease.
5. **Endometrial carcinoma**
 - a. Primary treatment as a single agent
 - i. With sequential radiation therapy (RT) and brachytherapy with or without surgery for extrauterine pelvic disease
 - ii. Consider following palliative hysterectomy with bilateral salpingo-oophorectomy with or without RT and hormonal therapy for extra-abdominal or liver disease.
 - b. Completely surgically staged patients as a single agent

- i. With or without sequential tumor-directed RT for stage IIIA, IIIB, and IIIC disease
- ii. With or without sequential RT for stage IV disease.
- c. Single agent
 - i. For low-grade or asymptomatic disseminated metastases that have progressed on hormonal therapy
 - ii. With or without sequential palliative radiation therapy (RT) for symptomatic, grade 2-3, or large volume metastases
 - iii. With sequential tumor-directed RT with or without brachytherapy for local recurrence in patients with disease confined to the vagina or in pelvic, para-aortic, or common iliac lymph nodes
 - iv. With or without sequential tumor-directed RT for microscopic upper abdominal or peritoneal recurrences
 - v. For local/regional recurrence in patients who have received prior external beam RT to site of recurrence.
- d. Adjuvant therapy as a single agent with or without sequential tumor-directed radiation therapy.

6. Hodgkin lymphoma

- a. Second-line or salvage therapy as a component of GVD (gemcitabine, vinorelbine, and liposomal doxorubicin) regimen prior to autologous stem cell rescue for progressive disease or for relapsed disease in patients initially treated with chemotherapy.

7. Non-Hodgkin's Lymphoma (NHL)

- a. Diffuse large B-cell lymphoma
 - i. First-line therapy in patients with poor left ventricular function as a component of RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) regimen with rituximab.
- b. Mycosis Fungoides/Sezary Syndrome
 - i. First-line chemotherapy as a single agent or as a component of GVD (gemcitabine, vinorelbine, and liposomal doxorubicin) regimen in patients with intention to proceed to transplant with any of the following:
 - a. stage IA-IIA MF with histologic evidence of folliculotropic or large cell transformation or stage IIB with generalized extent tumor, transformed, and/or folliculotropic disease in combination with skin-directed therapy
 - b. stage IV non-Sezary or visceral disease
 - c. refractory or progressive stage III MF or SS.
- c. Non-gastric MALT lymphoma
 - i. First-line therapy for MALT lymphomas coexistent with large cell lymphoma in patients with the indications for treatment and with poor left ventricular function as a component of RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) regimen.

- d. Primary cutaneous B-cell lymphoma
 - i. First-line therapy for primary cutaneous diffuse large B-cell lymphoma, leg type in patients with poor left ventricular function as a component of CDOP (cyclophosphamide, liposomal doxorubicin, vincristine, and prednisone) regimen with rituximab.
- e. Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders
 - i. As a single agent or as a component of GVD (gemcitabine, vinorelbine, and liposomal doxorubicin) regimen for relapsed or refractory.
- f. Peripheral T-Cell Lymphoma/Adult T-cell Leukemia/Lymphoma
 - i. Second-line or subsequent therapy for relapsed or refractory disease in patients with intention to proceed to transplant as a component of GVD (gemcitabine, vinorelbine, and liposomal doxorubicin) regimen.

8. Soft Tissue Sarcoma

- a. As a single agent for preoperative, adjuvant, unresectable, recurrent, or metastatic soft tissue sarcoma of the extremity/trunk or retroperitoneal/intraabdominal origins.

Exclusion Criteria: Doxil/Lipodox (liposomal doxorubicin) is not considered medically necessary when any of the following selection criteria is met:

1. Disease progression while taking Doxil/Lipodox (liposomal doxorubicin).
2. History of severe hypersensitivity reactions, including anaphylaxis, to standard doxorubicin (Adriamycin).
3. Concurrent use with another anthracycline.
4. Dosing exceeds single dose limit of Doxil/Lipodox (liposomal doxorubicin) 50 mg/m².
5. Dosing exceeds the total cumulative doses of 550 mg/m².
6. Members who have not progress after initial treatment of their KS, multiple myeloma or ovarian cancer.
7. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

IV. PROCEDURE

Requests for Doxil/Lipodox (liposomal doxorubicin) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. Dosage and Administration

- a. Aids related Kaposi's Sarcoma (KS): 20 mg/m² (doxorubicin equivalent) once every 3 weeks. Therapy should be continued for as long as patients remain responsive and tolerate the drug.
- b. Multiple Myeloma
 - i. In combination with bortexamib: 30 mg/m² IV infusion on DAY 4 ONLY. Cycles are repeated every 3 weeks until disease progression or unacceptable toxicity, for up to 8 cycles.

- ii. In combination with vincristine and dexamethasone: 40 mg/m² cycle is repeated every 4 weeks.
- c. Ovarian cancer: 50 mg/m² administered ONCE every 4 weeks as long as the tumor does NOT progress and the patient tolerates treatment.

2. Dosage Adjustments

- a. Palmar-plantar erythrodysesthesia
 - i. Grade 1 (mild erythema, swelling or desquamation not interfering with daily activities): If patient has had previous grade 3—4 toxicity, delay next course up to 2 weeks and decrease dose by 25%, otherwise follow normal schedule.
 - ii. Grade 2 (erythema, swelling or desquamation that interferes with, but does not preclude, daily activities or walking; small blisters or ulcerations less than 2 cm in diameter): Delay next course up to 2 weeks or until resolved to Grade 0—1. If resolved to Grade 0—1 within 2 weeks and there are no prior Grade 3—4, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3—4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval. If after 2 weeks, there is no resolution, discontinue pegylated liposomal doxorubicin.
 - iii. Grade 3 (blistering, ulceration or swelling interfering with walking or normal activities; cannot wear regular clothing): Delay next course up to 2 weeks or until resolved to Grade 0—1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks, there is no resolution, discontinue pegylated liposomal doxorubicin.
 - iv. Grade 4 (diffuse or local process causing infections or a bed ridden state or hospitalization): Delay next course up to 2 weeks or until resolved to Grade 0—1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks, there is no resolution, discontinue pegylated liposomal doxorubicin.
- b. For stomatitis
 - i. Grade 1 (painless ulcers, erythema, or mild soreness): If patient has had previous grade 3—4 toxicity, delay up to 2 weeks and decrease dose by 25%, otherwise follow original schedule.
 - ii. Grade 2 (painful erythema, edema, or ulcers, but can eat): Delay dosing up to 2 weeks or until resolved to Grade 0—1. If resolved to Grade 0—1 within 2 weeks, and there was no prior Grade 3—4 stomatitis, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3—4 toxicity, decrease dose by 25% and return to original dosing interval. If after 2 weeks, there is no resolution, discontinue pegylated liposomal doxorubicin.
 - iii. Grade 3 (painful erythema, edema or ulcers and cannot eat): Delay dosing up to 2 weeks or until resolved to Grade 0—1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks, there is no resolution, discontinue pegylated liposomal doxorubicin.
 - iv. Grade 4 (requires parenteral or enteral nutritional support): Delay dosing up to 2 weeks or until resolved to Grade 0—1. Decrease dose by 25% and return to original dosing interval. If after 2 weeks, there is no resolution, discontinue pegylated liposomal doxorubicin.

- c. For hematologic toxicity in patients with ovarian cancer or HIV-related Kaposi's sarcoma:
 - i. Grade 1 (ANC of 1500—1900/mm³, platelets \geq 75,000/mm³: No dose reduction
 - ii. Grade 2 (ANC of 1000-1499/mm³, platelets \geq 50,000/mm³ and $<$ 75,000/mm³: Wait until ANC \geq 1500 cells/mm³ and platelets \geq 75,000 cells/mm³; redose with no dose reduction.
 - iii. Grade 3 (ANC of 500—999/mm³, platelets \geq 25,000/mm³ and $<$ 50,000/mm³: Wait until ANC \geq 1500 cells/mm³ and platelets \geq 75,000 cells/mm³; redose with no dose reduction.
 - iv. Grade 4 (ANC $<$ 500/mm³, platelets $<$ 25,000/mm³): Wait until ANC \geq 1500 cells/mm³ and platelets \geq 75,000 cells/mm³; reduce dose by 25% or continue with full dose with colony-stimulating factor support.
- d. For hematologic toxicity in patients with multiple myeloma who are also treated with bortezomib:
 - i. ANC $<$ 500/mm³, platelets $<$ 25,000/mm³, or hemoglobin $<$ 8 g/dl on any day of drug administration after day 1 of each cycle: Do not administer for current cycle if before day 4. If after day 4, reduce subsequent doses by 25% if bortezomib is reduced for hematologic toxicity.
 - ii. ANC $<$ 1000/mm³ and fever \geq 38 degrees C: Do not administer for current cycle if before day 4. If after day 4, reduce next dose by 25%. Bortezomib dose alteration is also needed.
- e. For non-hematologic, drug-related, Grade 3 or 4 toxicity other than palmar-plantar erythrodyesthesia or stomatitis in patients with multiple myeloma who are also treated with bortezomib:
 - i. Wait until toxicity is less than Grade 2; reduce dose by 25% for all subsequent doses. Bortezomib dose alteration is also needed.
- f. Patients with Hepatic Impairment Dosing
 - i. Total bilirubin 1.2—3 mg/dl: reduce recommended dose of pegylated liposomal doxorubicin (Doxil) by 50%.
 - ii. Total bilirubin $>$ 3 mg/dl: reduce recommended dose of pegylated liposomal doxorubicin (Doxil) by 75%.
- g. Patients with Renal Impairment Dosing
 - i. Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

3. Monitoring

- a. Cardiotoxicity, during therapy or after discontinuation, may occur, increased risk with cumulative total anthracycline and anthracenediones doses exceeding 550 mg/m², or with lower (400 mg/m² doses in patients who have received radiotherapy to the mediastinal area or concomitant cyclophosphamide therapy; careful monitoring required
- b. Hepatic function, impaired; increased risk of drug toxicity; dosage adjustment necessary

- c. Infusion-associated reactions, acute and sometimes fatal allergic/anaphylactoid-like reactions (mostly occurring with first infusion), have been reported
- d. Myelosuppression, including fatal cases, have been reported, increased risk with concomitant use of drugs that cause bone marrow suppression; monitoring is required; dose reduction, delay, or discontinuation may be necessary
- e. Pregnancy should be avoided; known teratogen
- f. Substitution of liposomal doxorubicin for doxorubicin hydrochloride has resulted in severe side effects; do not substitute on a mg per mg basis
- g. Cardiovascular disease; increased risk of cardiotoxicity; use only when potential benefit outweighs the risk
- h. Concomitant use of other anticancer therapies; potentiation of toxicity has been reported, including hepatotoxicity of 6-mercaptopurine and cyclophosphamide-induced hemorrhagic cystitis
- i. Hand-foot syndrome, in some cases severe or debilitating, has occurred; may require discontinuation
- j. Radiation-induced toxicity to the myocardium, mucosae, skin, and liver, exacerbation of; has been reported
- k. Radiation recall reaction has been reported with liposomal doxorubicin administration following radiotherapy

V. APPROVAL AUTHORITY

1. Review – UM Department
2. Final Approval – UM Committee

VI. ATTACHMENTS

None

VII. REFERENCES

1. Doxil prescribing information. Janssen Products, LP Horsham, PA 2016.
2. Clinical Pharmacology Elsevier Gold Standard. 2016.
3. Micromedex® Healthcare Series: Thomson Micromedex, Greenwood Village, Co. 2016.
4. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium. 2016.
5. AHFS Drug Information. American Society of Health-Systems Pharmacists. Bethesda, MD. 2016.