09-J0000-91

Original Effective Date: 04/15/09

Reviewed: 04/08/15

Revised: 10/01/24

Subject: Doxorubicin HCl Liposome (Doxil®) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Liposomal doxorubicin formulations were developed to decrease the incidence of severe toxicity that has been observed with the conventional formulation of doxorubicin. The liposomal formulations incorporate doxorubicin into a liposomal carrier. In addition to the advantage of less toxicity, liposomal doxorubicin formulations are irritants, but not vesicants, upon extravasation. Liposomal doxorubicin (Doxil) has been studied extensively in persons with AIDS-related advanced Kaposi's sarcoma and refractory ovarian cancer. Liposomal doxorubicin was approved by the US Food and Drug Administration (FDA) in November 1995 as second-line treatment for Kaposi's sarcoma. Under priority review in 1999, the FDA approved liposomal doxorubicin for metastatic ovarian cancer that is refractory to cisplatin- and paclitaxel-based chemotherapy. The approval was extended in 2005 to include ovarian cancer that has progressed or recurred following platinum-based chemotherapy. Liposomal doxorubicin was granted orphan designation by the FDA for the treatment of ovarian cancer in 1998 and multiple myeloma in 2004. In May 2007, the FDA approved liposomal doxorubicin as combination therapy with bortezomib (Velcade) to treat persons with multiple myeloma who have received at least one prior therapy; efficacy of combination treatment was established in bortezomib-naïve subjects.

In 2012, due to a severe national shortage of Doxil, the FDA permitted temporary importation of Lipodox (doxorubicin hydrochloride liposome injection) by Sun Pharma Global FZE and its authorized distributor, Caraco Pharmaceutical Laboratories Ltd. The vials are manufactured in India at an FDA-inspected facility and contain the same active ingredient at the same concentration (2 mg/mL).

National Comprehensive Cancer Network (NCCN) guidelines support liposomal doxorubicin for the treatment of a variety of cancers including Kaposi's sarcoma, invasive breast cancer, multiple myeloma, ovarian cancer, soft tissue sarcoma, B-cell lymphomas, primary cutaneous lymphomas, T-cell lymphomas, Hodgkin lymphoma, and endometrial carcinoma.

POSITION STATEMENT:

Liposomal doxorubicin (Doxil) meets the definition of **medical necessity** when **EITHER** of the following are met ("1" or "2"):

1. **BOTH** of the following ("a" and "b"):
    a. Member has **ANY** of the following indications:
        i. Kaposi sarcoma (KS)
        ii. Desmoid tumor (a.k.a., aggressive fibromatosis)
        iii. Ovarian cancer (including fallopian tube carcinoma and primary peritoneal carcinoma)
        iv. Refractory, previously-treated ovarian cancer (including fallopian tube carcinoma and primary peritoneal carcinoma)
        v. Invasive breast cancer
        vi. Soft tissue sarcoma
        vii. Anaplastic rhabdomyosarcoma (a.k.a., pleomorphic rhabdomyosarcoma)
        viii. Angiosarcoma
        ix. Metastatic dermatofibrosarcoma protuberans (DFSP)
        x. B-cell lymphomas (including all subtypes such as multicentric Castleman's disease, diffuse large B-cell lymphoma, follicular lymphoma, MALT lymphomas, etc.)
        xi. Hodgkin lymphoma
        xii. Primary cutaneous lymphomas [including cutaneous anaplastic large cell lymphoma (ALCL), Mycosis Fungoides, Sezary Syndrome]
        xiii. Relapsed/refractory, previously-treated T-cell lymphomas [including adult T-cell leukemia/lymphoma (ATLL), hepatosplenic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified (NOS), enteropathy-associated T-cell lymphoma, monomorphic epitheliotropic intestinal T-cell lymphoma, nodal peripheral T-cell lymphoma with TFH phenotype, or follicular T-cell lymphoma]
        xiv. Uterine neoplasm (i.e., endometrial carcinoma, uterine sarcoma)
        xv. First-line treatment of multiple myeloma.
        xvi. Refractory, previously-treated multiple myeloma in combination with bortezomib
    b. The dosage does not exceed 50 mg/m^2 every 28 days (4 weeks) [more frequent dosing is acceptable as long as the cumulative dosage per 28 days is not greater than 50 mg/m^2, for example 20 or 30 mg/m^2 every 21 days (3 weeks) is acceptable]
2. Member has another FDA-approved or NCCN-supported diagnosis, and **BOTH** of the following criteria are met ("a" and "b"):
    a. **EITHER** of the following ("i" or "ii"):
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert), **AND** member meets any

additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

b. The dosage of liposomal doxorubicin does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: doxorubicin liposome injection is indicated for the treatment of ovarian cancer after failure of platinum-based chemotherapy, AIDS-related Kaposi's sarcoma after failure or intolerance of prior systemic chemotherapy, and in the treatment of multiple myeloma in combination with bortezomib in persons who have not previously received bortezomib and have received at least one prior therapy. Doxorubicin liposomal injection should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion related reactions occur, the rate of infusion should be increased to complete the infusion administration over 1 hour. Do **NOT** use with in-line filters or mix with other medications. Table 1 lists the FDA-approved indications and recommended dosage regimens. The maximum lifetime cumulative dose is 550 mg/m^2 in most persons; for those having received mediastinal radiation or other cardiotoxic drugs, the maximum lifetime cumulative dose is 400 mg/m^2.

Table 1

FDA-approved indications and dosage regimens	
Indication	**Dose**
AIDS-related Kaposi's sarcoma	20 mg/m^2 IV every 3 weeks until disease progression or unacceptable toxicity.
Multiple Myeloma	Following bortezomib administration, 30 mg/m^2 IV on day 4 every 3 weeks for eight cycles or until disease progression or unacceptable toxicity. (bortezomib: 1.3 mg/m^2 bolus on days 1, 4, 8 and 11)
Ovarian Cancer	50 mg/m^2 every 4 weeks until disease progression or unacceptable toxicity.
IV, intravenous	

Dose Adjustment

- **Hepatic Impairment:** the dose should be reduced if the bilirubin level is 1.2 mg/dL or greater. Specific dosage recommendations are not given in the package insert; however, the following can be used as a general guideline.

- Serum bilirubin 1.2 to 3 mg/dL: give ½ the normal dose
- Serum bilirubin greater than 3 mg/dL: give ¼ the normal dose.

- Toxicity: adverse reactions, such as hand-foot syndrome, hematologic toxicities, and stomatitis may be managed by dose delay and adjustments. Following the first appearance of a Grade 2 or higher adverse reaction, the dosing should be adjusted or delayed as described in the package insert. Once the dose has been reduced, it should not be increased at a later time.

Drug Availability: doxorubicin liposomal injection is supplied as a 20 mg/10mL and 50 mg/25 mL single-use vial.

PRECAUTIONS:

Boxed Warning

- Cardiotoxicity including myocardial damage that may lead to congestive heart failure may occur. Please refer to dosage and administration section for maximum lifetime cumulative dose recommendations.
- Acute infusion reactions have been reported in up to 10% of persons administered doxorubicin liposomal. Medications/emergency equipment to treat such reactions should be available for immediate use. The reactions are sometimes reversible upon terminating the infusion or slowing the infusion rate.

Contraindications

- Members who have a history of severe hypersensitivity reactions, including anaphylaxis, to doxorubicin HCl.

Warnings

- Do **NOT** substitute liposomal doxorubicin (Doxil) on a mg per mg basis with doxorubicin hydrochloride (Adriamycin).
- Do **NOT** administer as an undiluted suspension or as an intravenous bolus.
- Reduce the dose in members with hepatic dysfunction. Refer to dosage and administration section for additional information.
- Hand-Foot Syndrome: may require dose modification or discontinuation.
- Radiation recall reaction may occur.
- Doxorubicin can cause fetal harm when administered to pregnant women. Advise females and males of reproductive potential to use effective contraception during and for 6 months after treatment.
- Doxorubicin may potentiate the toxicity of other anticancer therapies.
- Complete blood counts, including platelet counts should be obtained frequently and at a minimum prior to each dose of doxorubicin.
- Secondary oral cancers, primarily squamous cell carcinoma, have been reported from post-marketing experience in patients with long-term (more than one year) exposure. Examine patients

at regular intervals for the presence of oral ulceration or with any oral discomfort that may be indicative of secondary oral cancer.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

Q2049	Injection, doxorubicin hydrochloride, liposomal, imported Lipodox, 10 mg
Q2050	Injection, doxorubicin hydrochloride, liposomal, not otherwise specified, 10 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

B10.89	Other human herpesvirus infection
C22.3	Angiosarcoma of liver
C44.99	Other specified malignant neoplasm of skin, unspecified
C46.0 – C46.9	Kaposi's sarcoma
C47.0 – C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48.0 – C49.9	Malignant neoplasm of retroperitoneum and peritoneum and other connective and soft tissue
C50.011 – 50.929	Malignant neoplasm of breast
C53.0	Malignant neoplasm of endocervix
C54.0 – C54.9	Malignant neoplasm of body of uterus
C55	Malignant neoplasm of uterus, part unspecified
C56.0 – C56.9	Malignant neoplasm of ovary
C57.0 – C57.9	Malignant neoplasm of other and unspecified female genital organs
C78.00	Secondary malignant neoplasm of unspecified lung
C81.00 – C81.99	Hodgkin lymphoma
C83.00 – C83.99	Non follicular lymphoma
C84.00 – C84.09	Mycosis fungoides
C84.10 - C84.19	Sézary disease
C84.40 - C84.49	Peripheral T-cell lymphoma, not elsewhere classified
C84.90 - C84.99	Mature T/NK-cell lymphomas, unspecified
C84.Z0 - C84.Z9	Other mature T/NK-cell lymphomas
C85.20 - C85.29	Mediastinal (thymic) large B-cell lymphoma
C86.10	Hepatosplenic T-cell lymphoma not having achieved remission
C86.20	Enteropathy-type (intestinal) T-cell lymphoma not having achieved remission
C86.60	Primary cutaneous CD30-positive T-cell proliferations not having achieved remission
C88.80	Other malignant immunoproliferative diseases not having achieved remission
C88.90	Malignant immunoproliferative disease, unspecified not having achieved remission
C90.00 – C90.32	Multiple myeloma and plasma cell leukemia
C91.50 – C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated)

D47.Z2	Castleman disease
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D48.1	Neoplasm of uncertain behavior of connective and other soft tissue

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) or Local Coverage Determination (LCD) were found at the time of the last guideline revised date. The prior LCD [Doxorubicin, Liposomal (Doxil/Lipodox), (L33722)] was retired effective 11/15/19.

DEFINITIONS:

No guideline specific definitions apply.

RELATED GUIDELINES:

Bortezomib Injection, 09-J0000-92
Carboplatin (Paraplatin) IV, 09-J0000-93
Nab-Paclitaxel Injection (Abraxane), 09-J1000-05
Oral Oncology Medications, 09-J3000-65
Rituximab Products, 09-J0000-59
Topotecan HCl (Hycamtin) IV, 09-J1000-02
Trastuzumab (Herceptin, biosimilars) and Trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) Injection, 09-J0000-86
Vinorelbine Tartrate (Navelbine) IV, 09-J1000-03

OTHER:

None applicable.

REFERENCES:

1. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2021. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 11/11/21.
2. Doxil (doxorubicin liposomal) [package insert]. Janssen Products, LP. Horsham (PA): August 2019.
3. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 11/11/21.

4. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and . Biologics Compendium. Accessed 11/11/21.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/08/15.

GUIDELINE UPDATE INFORMATION:

04/15/09	New Medical Coverage Guideline.
10/15/09	Revision to guideline; consisting of clarifying dosage and updating coding.
04/15/10	Review and revision to guideline; consisting of updating codes and references.
08/01/10	Revision to guideline; consisting of updating coding.
05/15/11	Review and revision to guideline; consisting of updating dosage section and references.
05/15/12	Review and revision to guideline; consisting of updating precautions, coding and references.
10/15/12	Revision to guideline; consisting of removing cervical cancer indication and updating coding.
01/01/13	Annual HCPCS Update; added J9002, removed J9001 and Q2048.
02/15/13	Revision to guideline; consisting of updating coding.
05/15/13	Review and revision to guideline; consisting of revising position statement to remove treatment of uterine sarcoma and adding endometrial carcinoma; revising and reformatting dosage/administration, precautions, and description sections; updating references and coding.
07/01/13	Revision to guideline; consisting of updating coding and Program Exceptions section.
12/15/13	Revision to guideline; consisting of adding new indication and updating coding.
01/01/14	Revision to guideline; consisting of code update.
05/15/14	Review and revision to guideline; consisting of updating position statement, references, and coding.
05/15/15	Review and revision to guideline; consisting of updating description, position statement and decision tree, dosage/administration, precautions, references, and coding.
10/01/15	Revision consisting of update to Program Exceptions section.
11/01/15	Revision: ICD-9 Codes deleted.
10/01/16	Revision: ICD-10 code updates.
12/15/21	Revision to guideline consisting of updating description, position statement, billing/coding, program exceptions, related guidelines, and references.
10/01/22	Revision: ICD-10 code updates.
10/01/24	Revision: ICD-10 code updates.