IMPORTANT REMINDER
This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description
Doxorubicin liposomal (Doxil, Lipodox) is a liposomal form of doxorubicin HCl (Adriamycin®). It is an intravenous anthracycline chemotherapy medication used in the treatment of certain cancers. This policy and the coverage criteria below do not apply to doxorubicin HCl (Adriamycin). Doxorubicin HCl (Adriamycin) does not require prior authorization.
Policy/Criteria

I. Most contracts require prior authorization approval of doxorubicin liposomal (Doxil, Lipodox) prior to coverage. Doxorubicin liposomal (Doxil, Lipodox) may be considered medically necessary when the following criteria below are met:

   A. A diagnosis of ovarian cancer, recurrent or progressive, after treatment with platin-based chemotherapy.

   OR

   B. A diagnosis of progressive (requires systemic therapy) Kaposi’s sarcoma (KS).

   OR

   C. A diagnosis of multiple myeloma (MM) after at least one prior therapy has been ineffective or not tolerated. (see Appendix 1 for therapy options)

   OR

   D. A diagnosis of cutaneous T-cell lymphoma (CTCL; such as Mycosis Fungoides, Sézary Syndrome) after treatment with gemcitabine unless ineffective, contraindicated, or not tolerated.

II. Administration, Quantity Limitations, and Authorization Period

   A. OmedaRx does not consider doxorubicin liposomal (Doxil, Lipodox) to be a self-administered medication.

   B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Doxorubicin liposomal (Doxil, Lipodox) is considered not medically necessary when used for breast cancer or soft tissue sarcomas.

IV. Doxorubicin liposomal (Doxil, Lipodox) is considered investigational when used for all other conditions, including but not limited to:

   A. Diffuse large B cell lymphoma (DLBCL).

   B. Hodgkin lymphoma.

   C. Mesothelioma.

   D. Uterine neoplasms, including uterine sarcoma and endometrial carcinoma.

Position Statement

- Doxorubicin liposomal (Doxil, Lipodox) is doxorubicin HCl (Adriamycin), an anthracycline topoisomerase inhibitor, encapsulated in fat (STEALTH® liposomes).

- Doxorubicin liposomal (Doxil, Lipodox) is approved for the treatment of ovarian cancer, multiple myeloma, and AIDS-related Kaposi’s sarcoma when front-line therapies are not effective.
Doxorubicin liposomal (Doxil, Lipodox) is included as one of two systemic front-line regimens for the treatment of cutaneous T-cell lymphoma (CTCL), a rare form of non-Hodgkin's lymphoma, a disease with few treatment options.

Doxorubicin liposomal (Doxil, Lipodox) has been studied in combination with other chemotherapy medications in breast cancer and soft tissue sarcomas; however, it has not been shown to be superior to doxorubicin (Adriamycin)-based regimens, or the many other less-costly established chemotherapy regimens used in these conditions.

Because doxorubicin liposomal (Doxil, Lipodox) is a unique formulation of doxorubicin HCl (Adriamycin), there is interest in using doxorubicin liposomal (Doxil, Lipodox) in a variety of other indications where standard doxorubicin HCl (Adriamycin) has been shown to be effective, such as uterine neoplasms and diffuse large B cell lymphoma. To date there is no reliable evidence to determine the relative clinical benefit of doxorubicin liposomal (Doxil, Lipodox) compared to generic doxorubicin HCl (Adriamycin) in these cancers, where use of generic doxorubicin is the standard of care. Like generic doxorubicin HCl (Adriamycin), doxorubicin liposomal (Doxil, Lipodox) is associated with serious adverse effects including myelosuppression, infusion reactions, and cardiotoxicity. There is no reliable evidence to allow conclusion that doxorubicin liposomal (Doxil, Lipodox) is safer than generic doxorubicin HCl (Adriamycin). The recommended total (lifetime) cumulative dose of doxorubicin (550 mg/m²) applies to all anthracyclines, including conventional and liposomal formulations of doxorubicin.

**Clinical Efficacy**

**OVARIAN CANCER**

- Doxorubicin liposomal (Doxil, Lipodox) has not been proven in reliable clinical studies to be more effective than alternative treatment options for recurrent ovarian cancer.
- Three unreliable, open-label, single-arm trials evaluating doxorubicin liposomal (Doxil, Lipodox) reported a combined response rate of 13.8% in patients who were refractory to paclitaxel and platinum agents. [1]
- One unreliable randomized clinical trial reported doxorubicin liposomal (Doxil, Lipodox) to be as effective as topotecan for recurrent ovarian cancer. [2]
- One large randomized trial comparing doxorubicin liposomal (Doxil, Lipodox) plus carboplatin with paclitaxel plus carboplatin demonstrated an improvement in progression free survival with doxorubicin liposomal (Doxil, Lipodox) (hazard ratio, 0.821; 95% CI, 0.72 to 0.94; P = .005). Overall survival data are not yet available. [3]
- The National Comprehensive Cancer Network (NCCN) lists doxorubicin liposomal (Doxil, Lipodox) among several acceptable therapies for the treatment of recurrent ovarian cancer in platinum-resistant patients. [4]

**KAPOSI'S SARCOMA**

- Kaposi's sarcoma (KS) is a low-grade vascular tumor associated with human herpes virus 8 (HHV-8) infection. In patients with AIDS, KS usually presents on the skin, but lesions can spread to the mouth, gastrointestinal tract, and the respiratory tract. [5]
- Systemic chemotherapy is typically reserved for patients with more advanced KS or when there is rapid disease progression. Typical treatment options include liposomal anthracyclines, paclitaxel, bleomycin, and vinorelbine. [5]

- A randomized study in 241 patients with AIDS-related KS demonstrated a superior response to doxorubicin liposomal (Doxil, Lipodox) than a combination of bleomycin and vincristine (58.7% versus 23.3%, p<0.001). However, the results of this study are unreliable because patients who were randomized to receive combination therapy were more likely to terminate treatment early and therefore fewer completed the full six cycles of treatment (30.8% v 55.4%). [6]

- A Cochrane review concluded that response rates with liposomal doxorubicin (Doxil, Lipodox) are superior to standard chemotherapy (bleomycin and vincristine) in patients with Kaposi’s sarcoma. There was no difference in the relative risk of death or in adverse events between the different treatments. [7]

- In an unreliable trial in 73 patients with advanced AIDS-related KS who had no prior systemic therapy, similar tumor response rates were reported with paclitaxel and doxorubicin liposomal (Doxil, Lipodox). [8]

MULTIPLE MYELOMA

- Doxorubicin liposomal (Doxil, Lipodox) has not been proven to be more effective than alternative treatment options for multiple myeloma. However, it is one of the three preferred therapies for previously treated multiple myeloma.

- An unreliable, open-label, phase III study compared doxorubicin liposomal (Doxil, Lipodox) plus bortezomib with bortezomib alone in 646 subjects with MM who were refractory to initial treatment or had progressive disease after response to one or more prior therapies. [9]

  * The median time-to-progression for the doxorubicin liposomal (Doxil, Lipodox) plus bortezomib and bortezomib alone groups was 9.3 months and 6.5 months, respectively. The risk of developing disease progression was reduced by 45% with doxorubicin liposomal (Doxil, Lipodox) plus bortezomib (HR = 1.82; 95% CI: 1.41 – 2.35; p = 0.000004).

  * The overall response rates (complete plus partial response rate) for doxorubicin liposomal (Doxil) plus bortezomib and bortezomib alone were similar (44% and 41%, respectively).

- In a small, single-arm, open-label trial, combination therapy with doxorubicin liposomal (Doxil, Lipodox), bortezomib, and dexamethasone in patients newly diagnosed with multiple myeloma showed some activity in tumor response rate. Larger, well-controlled comparative trials are needed to determine relative efficacy and safety of this treatment. [10]

- The NCCN guidelines list several options for salvage therapy in multiple myeloma, including bortezomib (Velcade), lenalidomide (Revlimid), and doxorubicin liposomal injection (Doxil, Lipodox) (all Category 1 options). [11]
CUTANEOUS T-CELL LYMPHOMAS (e.g. Cutaneous T-cell lymphomas (e.g. Mycosis Fungoides, Sézary Syndrome)
- Gemcitabine and liposomal doxorubicin (Doxil, Lipodox) are among the two first-line systemic therapies for certain stages of Mycosis Fungoides (MF) and Sézary Syndrome (SS). [19]
- There are no large, well-controlled trials evaluating any therapy in MF or SS, both of which are rare forms of non-Hodgkin’s lymphomas.
- The NCCN non-Hodgkin’s lymphoma guideline lists doxorubicin liposomal (Doxil, Lipodox) among several systemic treatment options for the treatment of CTCL. [19] All of these options are listed as NCCN category 2A recommendations meaning the quality of evidence is low but there was consensus among oncologists on the panel for inclusion on the guideline.

OTHER CANCERS – BREAST CANCER and SOFT TISSUE SARCOMA
Doxorubicin liposomal injection (Doxil, Lipodox) has been studied for treatment of breast cancer and soft tissue sarcomas. [12] Although doxorubicin liposomal injection (Doxil, Lipodox) is safe and effective for these indications, it has not been proven to be superior to many other less costly alternatives. Therefore, the use of Doxorubicin liposomal injection (Doxil, Lipodox) for treatment of breast cancer or soft tissue sarcomas is considered not medically necessary.

Breast Cancer
- Doxorubicin liposomal (Doxil, Lipodox) has not been shown to be superior to many available alternative therapies in patients with breast cancer, as monotherapy, including doxorubicin HCL (Adriamycin), yet is more costly. [13-15]
- Adding doxorubicin liposomal (Doxil, Lipodox) to other chemotherapy has not been shown to improve overall survival in patients with breast cancer, compared to monotherapy. The addition of doxorubicin liposomal (Doxil, Lipodox) to docetaxel for the treatment of advanced breast cancer did not result in improved overall survival compared to monotherapy with docetaxel in a large, randomized, controlled trial (median 20.5 month vs. 20.6 months). [16]
- The NCCN breast cancer guideline lists liposomal doxorubicin (Doxil, Lipodox) among possible preferred single agent treatment options for recurrent or metastatic breast cancer. Other options include but are not limited to anthracyclines (doxorubicin HCl (Adriamycin), epirubicin), taxanes (e.g. paclitaxel, docetaxel, albumin-bound paclitaxel), anti-metabolites (gemcitabine, capecitabine) and microtubule inhibitors (vinorelbine, eribulin). [17]
- The NCCN does not recognize doxorubicin liposomal (Doxil, Lipodox) as an option among the many preferred combination chemotherapy regimens; however other anthracyclines [doxorubicin HCL (Adriamycin) and epirubicin] are in several preferred combination regimens. Doxorubicin liposomal (Doxil, Lipodox) is listed among several different single agent options for the treatment of recurrent or metastatic breast cancer. [17]
Soft Tissue Sarcomas

- There are many systemic therapies used in the treatment of soft tissue sarcomas. The majority of these treatment options are generic medications, which generally cost less than branded options. All treatment options are listed as category 2A recommendations on the NCCN Soft Tissue Sarcoma guideline. \[^{18}\]

  * Combination generic regimens include: doxorubicin/dacarbazine, doxorubicin/ifosfamide/mesna, ifosfamide/epirubicin/mesna, gemcitabine/docetaxel, and gemcitabine/vinorelbine.

  * Single-agent generic regimens include: doxorubicin, ifosfamide, epirubicin, gemcitabine, and dacarbazine.

  * Branded options include liposomal doxorubicin (Doxil, Lipodox) and temozolomide.

INVESTIGATIONAL USES

- Anthracyclines, including doxorubicin liposomal (Doxil, Lipodox), are recognized as standard of care chemotherapy options for a variety of cancers, including but not limited to uterine sarcoma, endometrial carcinoma, Hodgkin lymphoma, and diffuse large B cell lymphoma (DLBCL). \[^{22}\]

- Although the use of doxorubicin liposomal (Doxil, Lipodox) is recognized by the NCCN as a treatment option, there is insufficient evidence to establish that doxorubicin liposomal (Doxil, Lipodox) is safe or effective in these other cancers. \[^{22}\] The evidence for use in these various cancers is limited to Phase 2 trials. \[^{19,24,25}\]

- In addition, the dose of doxorubicin liposomal (Doxil, Lipodox) has not been clearly established. More research is needed to establish the safety, efficacy, and appropriate dose of doxorubicin liposomal (Doxil, Lipodox) in these other cancers.

- Because the safety and efficacy of the liposomal formulation of doxorubicin (Doxil, Lipodox) is uncertain and the dose is unknown, the use of doxorubicin liposomal (Doxil, Lipodox) for these cancers not specified in the coverage criteria is considered investigational.

- The NCCN recognizes the use of liposomal doxorubicin (Doxil, Lipodox) as one of the possible chemotherapy regimens for uterine sarcoma, endometrial carcinoma, Hodgkin lymphoma, and diffuse large B cell lymphoma (DLBCL), along with the less costly generic doxorubicin. \[^{19,26,27}\]

Mesothelioma

- In a single-arm Phase II study (n=173) for the treatment of malignant pleural mesothelioma, doxorubicin liposomal (Doxil, Lipodox) in combination with carboplatin and gemcitabine resulted in a treatment response for 32.4% of patients. Larger, randomized Phase III trials are needed to establish the safety and efficacy of doxorubicin liposomal injection (Doxil, Lipodox) in this indication. \[^{20}\]

- The use of doxorubicin liposomal (Doxil, Lipodox) is not recognized by the NCCN guidelines for treatment of mesothelioma. \[^{23}\]
OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN guidelines.

Safety
- The most common adverse reactions (>20%) reported with doxorubicin liposomal injection (Doxil, Lipodox) include asthenia, fatigue, fever, anorexia, nausea, vomiting, stomatitis, diarrhea, constipation, hand and foot syndrome, rash, neutropenia, thrombocytopenia and anemia. [1]
- Doxorubicin liposomal injection (Doxil, Lipodox) carries a Box Warning for infusion reactions, myelosuppression, cardiotoxicity, and liver impairment. [1]
- Medications to treat infusion reactions as well as emergency equipment should be available during the infusion for immediate use. [1]
- Despite the perceived superior tolerability, there is no evidence that doxorubicin liposomal injection (Doxil, Lipodox) has superior tolerability to generic doxorubicin HCl (Adriamycin), including for rates of alopecia, nausea, vomiting, neutropenia, or associated complications. In addition, there is no evidence that the use of doxorubicin liposomal injection (Doxil, Lipodox) reduces the need for supportive care therapies, including antiemetics, such as NK1 receptor antagonists or 5HT3s, or myeloid growth factors like filgrastim (Neupogen, Granix, or Zarxio) or pegfilgrastim (Neulasta).

CARDIOTOXICITY
There is no reliable evidence to allow conclusion that doxorubicin liposomal injection (Doxil, Lipodox) is safer than generic doxorubicin HCl (Adriamycin). Further research is needed to reliably determine the relative clinical efficacy and safety of both doxorubicin formulations, in breast cancer as well as other cancers.
- All anthracyclines (doxorubicin, doxorubicin liposomal, epirubicin) are cardiotoxic. Cardiotoxicity can be categorized as subclinical (identified by diagnostic tests) or clinical (manifesting as symptoms of clinical heart failure, due to myocardial damage and left ventricular function impairment). Cardiotoxicity can manifest early (develops during anthracycline therapy or during first year after treatment) or late (manifesting at least one year after completion of therapy). [21]
- Many different factors may increase the risk in developing cardiotoxicity. These may include the type of anthracycline used, the cumulative anthracycline dose, radiation therapy in the region of the heart, the type of tumor, exposure to other cardiotoxic chemotherapy (e.g. cyclophosphamide, trastuzumab) or presence of pre-existing heart damage. Additionally, the risk appears to be higher in females, children, and the elderly. [21]
- As the cumulative dose of doxorubicin increases (liposomal or conventional formulations), the risk of cardiotoxicity increases. The currently recommended maximum lifetime cumulative dose of doxorubicin is 550 mg/m². In patients who have received radiotherapy to the chest or are receiving other potential cardiotoxins (such as cyclophosphamide or trastuzumab), a lower maximum cumulative dose of 400 mg/m² may be used. [1]
- Per the Doxil prescribing information, calculation of the total cumulative dose should include prior anthracyclines and anthracenediones, including liposomal and conventional formulations. [1] Because doxorubicin liposomal injection (Doxil, Lipodox) contains doxorubicin and counts towards the lifetime cumulative dose of doxorubicin, the use of doxorubicin liposomal injection (Doxil, Lipodox) in patients at or near their lifetime maximum dose of doxorubicin is not recommended and is considered investigational.

- Similar to generic doxorubicin HCl (Adriamycin), the risks and benefits of doxorubicin liposomal injection (Doxil, Lipodox) should be carefully considered prior to use in patients with pre-existing cardiovascular disease. However, there is no conclusive evidence that doxorubicin liposomal injection (Doxil, Lipodox) is safer than generic doxorubicin HCl (Adriamycin) in patients with pre-existing cardiovascular disease or in those at high risk of cardiotoxicity.

- There is no available comparative safety evidence to conclude relative safety of one doxorubicin formulation over the other in patients with cancer other than breast cancer. The evidence is limited to Phase 2 trials or trials without safety as a powered endpoint.

  * A 2010 Cochrane review examined the available evidence regarding comparative cardiotoxicity of anthracyclines. [21] The authors concluded that doxorubicin liposomal injection (Doxil, Lipodox) is associated with a lower rate of clinical and subclinical cardiotoxicity than conventional (generic) doxorubicin HCl. However, there are notable flaws in the evidence that limit reliability of this conclusion:
    - The comparative evidence was limited to Phase 2 trials or trials without safety as a powered endpoint.
    - Only patients with metastatic breast cancer were included in the meta-analysis. There is no reliable information to establish relative safety of the two formulations of doxorubicin in patients with other types of cancer.
    - Other notable flaws affecting reliability include lack of blinding, uncertain blinding of assessors of heart damage, and missing information regarding concealment of allocation.

  * Recent systematic review and compendium resources suggest that there is conclusive evidence that doxorubicin liposomal injection (Doxil, Lipodox) is less cardiotoxic and can be given in higher cumulative doses (than generic doxorubicin HCl (Adriamycin), with lower rate of heart failure and myocardial damage. [28]
    - However, unlike the Cochrane analysis which evaluated RCT evidence, these conclusions are based on very-low quality, non-RCT evidence.
    - The evidence consists of case reports and observational trials of very small numbers of patients (1 to 16 patients) and no control arm to establish relative safety, [29-32] along with two larger retrospective analyses (n=42 to 78). [33,34]
    - Given the flaws, all these trials were excluded from the Cochrane review analysis, as the results are considered unreliable for establishing any cause-and-effect or relative safety.
Appendix 1:

**Preferred Regimens for Primary Treatment of Multiple Myeloma** \(^{[1][a,b]}\)

<table>
<thead>
<tr>
<th>Regimen</th>
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<tbody>
<tr>
<td>bortezomib (Velcade)/dexamethasone (category 1)</td>
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<tr>
<td>bortezomib (Velcade)/cyclophosphamide (Cytoxan)/dexamethasone</td>
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<tr>
<td>bortezomib (Velcade)/doxorubicin/dexamethasone (category 1)</td>
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<td>bortezomib (Velcade)/lenalidomide (Revlimid)/dexamethasone (RVD)</td>
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<tr>
<td>bortezomib (Velcade)/thalidomide/dexamethasone (category 1)</td>
</tr>
<tr>
<td>lenalidomide (Revlimid)/dexamethasone (category 1)</td>
</tr>
<tr>
<td>melphalan/prednisone/bortezomib (Velcade) (MPB) (category 1)</td>
</tr>
<tr>
<td>melphalan/prednisone/thalidomide (MPT) (category 1)</td>
</tr>
<tr>
<td>melphalan/prednisone/lenalidomide (Revlimid) (MPL) (category 1)</td>
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**Other regimens:** \(^{a,b}\)

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<tr>
<td>thalidomide/dexamethasone (category 2B)</td>
</tr>
<tr>
<td>vincristine/doxorubicin/dexamethasone (VAD) (category 2B)</td>
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</table>

\(^a\) All therapies listed above are NCCN category 2A recommendations unless otherwise indicated (Category 2A: lower quality evidence but uniform consensus among panel; Category 2B: lower quality evidence and nonuniform consensus among panel but no major disagreement).


**Cross References**

- Avastin®, bevacizumab, Medication Policy Manual, Policy No. dru215
- Folotyn®, pralatrexate, Medication Policy Manual, Policy No. 197
- Istodax®, romidepsin, Medication Policy Manual, Policy No. dru198
- Kyprolis®, carfilzomib Medication Policy Manual, Policy No. dru282
- Pomalyst®, pomalidomide, Medication Policy Manual, Policy No. dru293
- Revlimid®, lenalidomide, Medication Policy Manual, Policy No. dru127
- Velcade®, bortezomib, Medication Policy Manual, Policy No. dru190
- Zolinza®, vorinostat, Medication Policy Manual, Policy No. dru143
Cross References

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<th>Description</th>
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<tbody>
<tr>
<td>HCPCS</td>
<td>Q2050</td>
<td>Injection, doxorubicin hydrochloride, all lipid formulations (such as Doxil, Lipodox), 10 mg</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J9000</td>
<td>Injection, doxorubicin HCl (for \textit{generic} Adriamycin formulation)</td>
</tr>
</tbody>
</table>

References

5. Groopman JE. AIDS-related Kaposi’s sarcoma: Clinical features and treatment. In: UpToDate, Ross ME (Ed), UpToDate, Waltham, MA, 2011.


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