HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DOXIL safely and effectively. See full prescribing information for DOXIL.

DOXIL® (doxorubicin HCl liposome injection) for intravenous infusion
Initial U.S. Approval: 1995

WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, SUBSTITUTION

See full prescribing information for complete boxed warning.

- **Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m^2. Cardiac toxicity may also occur at lower cumulative doses with mediastinal irradiation or concurrent cardiotoxic agents (5.1).**
- **Acute infusion-related reactions, sometimes reversible upon terminating or slowing infusion, occurred in up to 10% of patients. Serious and sometimes fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications/emergency equipment to treat such reactions should be available for immediate use (5.2).**
- **Severe myelosuppression may occur (5.3)**
- **Reduce dosage in patients with impaired hepatic function (2.6).**
- **Accidental substitution of DOXIL resulted in severe side effects. Do not substitute on mg per mg basis with doxorubicin HCl (2.1).**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Multiple Myeloma (1.3)	5/2007
Dosage and Administration, Multiple Myeloma (2.4)	5/2007

----------INDICATIONS AND USAGE----------

DOXIL is an anthracycline topoisomerase inhibitor indicated for:

- **Ovarian cancer (1.1)**

After failure of platinum-based chemotherapy.

- **AIDS-related Kaposi's Sarcoma (1.2)**

After failure of prior combination chemotherapy or intolerance to such therapy. Results are based on objective response rate; no results are available from controlled trials that demonstrate clinical benefit.

- **Multiple Myeloma (1.3)**

In combination with bortezomib in patients who have not previously received bortezomib and have received at least one prior therapy.

----------DOSAGE AND ADMINISTRATION----------

Administer DOXIL at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion related reactions occur, increase rate of infusion to complete administration over 1 hour. Do not administer as bolus injection or undiluted solution (2.1).

- **Ovarian cancer:** 50 mg/m^2 IV every 4 weeks for 4 courses minimum (2.2)
- **AIDS-related Kaposi's Sarcoma:** 20 mg/m^2 IV every 3 weeks (2.3)
- **Multiple Myeloma:** 30 mg/m^2 IV on day 4 following bortezomib which is administered at 1.3 mg/m^2 bolus on days 1, 4, 8 and 11, every 3 weeks (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Single dose vial: 20 mg/10 mL and 50 mg/30 mL (3)

----------CONTRAINDICATIONS----------

- Hypersensitivity reactions to a conventional formulation of doxorubicin HCl or the components of DOXIL (4, 5.2)
- Nursing mothers (4, 8.3)

----------WARNINGS AND PRECAUTIONS----------

- Hand-Foot Syndrome may occur. Dose modification or discontinuation may be required (5.4)
- Radiation recall reaction may occur (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>20%) are asthenia, fatigue, fever, anorexia, nausea, vomiting, stomatitis, diarrhea, constipation, hand and foot syndrome, rash, neutropenia, thrombocytopenia and anemia (6).

To report SUSPECTED ADVERSE REACTIONS contact Ortho Biotech Products, LP at (888) 227-5624 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- DOXIL may interact with drugs known to interact with conventional formulations of Doxorubicin HCl. (7)

----------USE IN SPECIFIC POPULATIONS----------

- DOXIL can cause fetal harm when used during pregnancy. (5.6, 8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 05/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: INFUSION REACTIONS, MYELOSUPPRESSION, CARDIOTOXICITY, LIVER IMPAIRMENT, ACCIDENTAL SUBSTITUTION

1. **The use of DOXIL (doxorubicin HCl liposome injection) may lead to cardiac toxicity. Myocardial damage may lead to congestive heart failure and may occur as the total cumulative dose of doxorubicin HCl approaches 550 mg/m^2. In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at a starting dose of 50 mg/m^2 every 4 weeks. At all cumulative anthracycline doses between 450-500 mg/m^2 or between 500-550 mg/m^2, the risk of cardiac toxicity for patients treated with DOXIL was 11%. Prior use of other anthracyclines or anthracenediones should be included in calculations of total cumulative dosage. Cardiac toxicity may also occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy *[see Warnings and Precautions (5.1)]*.**

2. **Acute infusion-related reactions including, but not limited to, flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension have occurred in up to 10% of patients treated with DOXIL. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. DOXIL should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions *[see Warnings and Precautions (5.2)]*.**

3. **Severe myelosuppression may occur *[see Warnings and Precautions (5.3)]*.**

4. **Dosage should be reduced in patients with impaired hepatic function *[see Dosage and Administration (2.6) and Use in Specific Populations (8.6)]*.**

5. **Accidental substitution of DOXIL for doxorubicin HCl has resulted in severe side effects. DOXIL should not be substituted for doxorubicin HCl on a mg per mg basis *[see Dosage and Administration (2.1)]*.**

1 INDICATIONS AND USAGE

1.1 Ovarian Cancer

DOXIL (doxorubicin HCl liposome injection) is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy.

1.2 AIDS-Related Kaposi's Sarcoma

DOXIL is indicated for the treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.

The treatment of patients with AIDS-related Kaposi's sarcoma is based on objective tumor response rates. No results are available from controlled trials that demonstrate a clinical benefit resulting from this treatment, such as improvement in disease-related symptoms or increased survival.

1.3 Multiple Myeloma

DOXIL in combination with bortezomib is indicated for the treatment of patients with multiple myeloma who have not previously received bortezomib and have received at least one prior therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Usage and Administration Precautions

Liposomal encapsulation can substantially affect a drug's functional properties relative to those of the unencapsulated drug. Therefore DO NOT SUBSTITUTE one drug for the other.

Do not administer as a bolus injection or an undiluted solution. Rapid infusion may increase the risk of infusion-related reactions *[see Warnings and Precautions (5.2)]*. DOXIL must not be given by the intramuscular or subcutaneous route.

Until specific compatibility data are available, it is not recommended that DOXIL be mixed with other drugs.

DOXIL should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of DOXIL, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction.

2.2 Patients With Ovarian Cancer

DOXIL (doxorubicin HCl liposome injection) should be administered intravenously at a dose of 50 mg/m^2 (doxorubicin HCl equivalent) at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related adverse reactions are observed, the rate of infusion can be increased to complete administration of the drug over one hour. The patient should be dosed once every 4 weeks, for as long as the patient does not progress, shows no evidence of cardiotoxicity *[see Warnings and Precautions (5.1)]*, and continues to tolerate treatment. A minimum of 4 courses is recommended because median time to response in clinical trials was 4 months. To manage adverse reactions such as hand-foot syndrome (HFS), stomatitis,

or hematologic toxicity the doses may be delayed or reduced *[see Dosage and Administration (2.5)]*. Pretreatment with or concomitant use of antiemetics should be considered.

2.3 Patients With AIDS-Related Kaposi's Sarcoma

DOXIL (doxorubicin HCl liposome injection) should be administered intravenously at a dose of 20 mg/m^2 (doxorubicin HCl equivalent). An initial rate of 1 mg/min should be used to minimize the risk of infusion-related reactions. If no infusion-related adverse reactions are observed, the infusion rate should be increased to complete the administration of the drug over one hour. The dose should be repeated once every three weeks, for as long as patients respond satisfactorily and tolerate treatment.

2.4 Patients With Multiple Myeloma

Bortezomib is administered at a dose of 1.3 mg/m^2 as intravenous bolus on days 1, 4 , 8 and 11, every three weeks. DOXIL 30 mg/m^2 should be administered as a 1-hr intravenous infusion on day 4 following bortezomib. With the first DOXIL dose, an initial rate of 1 mg/min should be used to minimize the risk of infusion-related reactions. If no infusion-related adverse reactions are observed, the infusion rate should be increased to complete the administration of the drug over one hour. Patients may be treated for up to 8 cycles until disease progression or the occurrence of unacceptable toxicity.

2.5 Dose Modification Guidelines

DOXIL exhibits nonlinear pharmacokinetics at 50 mg/m^2; therefore, dose adjustments may result in a non-proportional greater change in plasma concentration and exposure to the drug *[see Clinical Pharmacology (12.3)]*.

Patients should be carefully monitored for toxicity. Adverse reactions, such as HFS, hematologic toxicities, and stomatitis may be managed by dose delays and adjustments. Following the first appearance of a Grade 2 or higher adverse reactions, the dosing should be adjusted or delayed as described in the following tables. Once the dose has been reduced, it should not be increased at a later time.

Recommended Dose Modification Guidelines

Table 1: Hand-Foot Syndrome (HFS)

Toxicity Grade	Dose Adjustment
1 (mild erythema, swelling, or desquamation not interfering with daily activities)	**Redose unless patient has experienced previous Grade 3 or 4 HFS.** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, DOXIL should be discontinued. If resolved to Grade 0-1 within 2 weeks, and there are no prior Grade 3-4 HFS, 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.
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 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, DOXIL should be discontinued.
4 (diffuse or local process causing infectious complications, or a bed ridden state or hospitalization)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, DOXIL should be discontinued.

Table 2: Hematological Toxicity

Grade	ANC	Platelets	Modification
1	1,500 – 1,900	75,000 - 150,000	Resume treatment with no dose reduction
2	1,000 - <1,500	50,000 - <75,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose with no dose reduction
3	500 – 999	25,000 - <50,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose with no dose reduction
4	<500	<25,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose at 25% dose reduction or continue full dose with cytokine support

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