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*

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HELSINN EXHIBIT 2102
Azurity Pharmaceuticals, Inc. v. Helsinn Healthcare S.A.
IPR2025-00947

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

Table 3: Stomatitis

Toxicity Grade	Dose Adjustment
1 (painless ulcers, erythema, or mild soreness)	**Redose unless patient has experienced previous Grade 3 or 4 toxicity.** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2 (painful erythema, edema, or ulcers, but can eat)	**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 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, continue treatment with a 25% dose reduction and return to original dose interval.
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 dose interval. If after 2 weeks there is no resolution, DOXIL should be discontinued.
4 (requires parenteral or enteral support)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to DOXIL original dose interval. If after 2 weeks there is no resolution, DOXIL should be discontinued.

Multiple Myeloma

For patients treated with DOXIL in combination with bortezomib who experience hand-foot syndrome or stomatitis, the DOXIL dose should be modified as described in Tables 1 and 3 above. Table 4 describes dosage adjustments for DOXIL and bortezomib combination therapy. For bortezomib dosing and dosage adjustments, see manufacturer's prescribing information.

Table 4: Dosage adjustments for DOXIL + bortezomib combination therapy

Patient status	DOXIL	bortezomib
Fever ≥38°C and ANC <1,000/mm^3	Do not dose this cycle if before Day 4; if after Day 4, reduce next dose by 25%.	Reduce next dose by 25%
On any day of drug administration after Day 1 of each cycle: Platelet count <25,000/mm^3 Hemoglobin <8g/dL ANC <500/mm^3	Do not dose this cycle if before Day 4; if after Day 4 reduce next dose by 25% in the following cycles if bortezomib is reduced for hematologic toxicity.	Do not dose; if 2 or more doses are not given in a cycle, reduce dose by 25% in following cycles.
Grade 3 or 4 non-hematologic drug related toxicity	Do not dose until recovered to Grade <2 and reduce dose by 25% for all subsequent doses.	Do not dose until recovered to Grade <2 and reduce dose by 25% for all subsequent doses.
Neuropathic pain or peripheral neuropathy	No dosage adjustments.	See bortezomib manufacturer's prescribing information for dosage adjustments in patients with neuropathic pain.

2.6 Patients With Impaired Hepatic Function

Limited clinical experience exists in treating patients with hepatic impairment with DOXIL. Based on experience with doxorubicin HCl, it is recommended that the DOXIL dosage be reduced if the bilirubin is elevated as follows: serum bilirubin 1.2 to 3.0 mg/dL - give ½ normal dose; serum bilirubin > 3 mg/dL - give ¼ normal dose.

No information, including dosage adjustments, is available for patients with multiple myeloma with hepatic impairment.

2.7 Preparation for Intravenous Administration

Each 10-mL vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/mL.

Each 30-mL vial contains 50 mg doxorubicin HCl at a concentration of 2 mg/mL.

DOXIL doses up to 90 mg must be diluted in 250 mL of 5% Dextrose Injection, USP prior to administration. Doses exceeding 90 mg should be diluted in 500 mL of 5% Dextrose Injection, USP prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in DOXIL. Diluted DOXIL should be refrigerated at 2°C to 8°C (36°F to 46°F) and administered within 24 hours.

Do not use with in-line filters.

Do not mix with other drugs.

Do not use with any diluent other than 5% Dextrose Injection.

Do not use any bacteriostatic agent, such as benzyl alcohol.

DOXIL is not a clear solution but a translucent, red liposomal dispersion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

Rapid flushing of the infusion line should be avoided.

2.8 Procedure for Proper Handling and Disposal

Caution should be exercised in the handling and preparation of DOXIL.

The use of gloves is required.

If DOXIL comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

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. **DOXIL must not be given by the intramuscular or subcutaneous route.**

DOXIL should be handled and disposed of in a manner consistent with other anticancer drugs. Several guidelines on this subject exist *[see References (15)]*.

3 DOSAGE FORMS AND STRENGTHS

- 20 mg/10 mL single use vial
- 50 mg/30 mL single use vial

4 CONTRAINDICATIONS

DOXIL (doxorubicin HCl liposome injection) is contraindicated in patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin HCl or the components of DOXIL *[see Warnings and Precautions (5.2)]*.

DOXIL is contraindicated in nursing mothers *[see Use in Specific Populations (8.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiac Toxicity

Special attention must be given to the risk of myocardial damage from cumulative doses of doxorubicin HCl. Acute left ventricular failure may occur with doxorubicin, particularly in patients who have received a total cumulative dosage of doxorubicin exceeding the currently recommended limit of 550 mg/m^2. Lower (400 mg/m^2) doses appear to cause heart failure in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide.

Prior use of other anthracyclines or anthracenodiones should be included in calculations of total cumulative dosage. Congestive heart failure or cardiomyopathy may be encountered after discontinuation of anthracycline therapy. Patients with a history of cardiovascular disease should be administered DOXIL only when the potential benefit of treatment outweighs the risk.

Cardiac function should be carefully monitored in patients treated with DOXIL. The most definitive test for anthracycline myocardial injury is endomyocardial biopsy. Other methods, such as echocardiography or multigated radionuclide scans, have been used to monitor cardiac function during anthracycline therapy. Any of these methods should be employed to monitor potential cardiac toxicity in patients treated with DOXIL. If these test results indicate possible cardiac injury associated with DOXIL therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

In a clinical study in patients with advanced breast cancer, 250 patients received DOXIL at 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%. In this study, cardiotoxicity was defined as a decrease of >20% from baseline if the resting left ventricular ejection fraction (LVEF) remained in the normal range, or a decrease of >10% if the resting LVEF became abnormal (less than the institutional lower limit of normal). The data on left ventricular ejection fraction (LVEF) defined cardiotoxicity and congestive heart failure (CHF) are in the table below.

Table 5: Number of Patients With Advanced Breast Cancer

	DOXIL (n=250)
Patients who Developed Cardiotoxicity (LVEF Defined)	10
Cardiotoxicity (With Signs & Symptoms of CHF)	0
Cardiotoxicity (no Signs & Symptoms of CHF)	10
Patients With Signs and Symptoms of CHF Only	2

In the randomized multiple myeloma study, the incidence of heart failure events (ventricular dysfunction, cardiac failure, right ventricular failure, congestive cardiac failure, chronic cardiac

failure, acute pulmonary edema and pulmonary edema) was similar in the DOXIL+bortezomib group and the bortezomib monotherapy group, 3% in each group. LVEF decrease was defined as an absolute decrease of ≥15% over baseline or a ≥5% decrease below the institutional lower limit of normal. Based on this definition, 25 patients in the bortezomib arm (8%) and 42 patients in the DOXIL + bortezomib arm (13%) experienced a reduction in LVEF.

5.2 Infusion Reactions

Acute infusion-related reactions were reported in 7.1% of patients treated with DOXIL in the randomized ovarian cancer study. These reactions were characterized by one or more of the following symptoms: flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension. 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 resolved when the rate of infusion was slowed. In this study, two patients treated with DOXIL (0.8%) discontinued due to infusion-related reactions. In clinical studies, six patients with AIDS-related Kaposi's sarcoma (0.9%) and 13 (1.7%) solid tumor patients discontinued DOXIL therapy because of infusion-related reactions.

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.

The majority of infusion-related events occurred during the first infusion. Similar reactions have not been reported with conventional doxorubicin and they presumably represent a reaction to the DOXIL liposomes or one of its surface components.

The initial rate of infusion should be 1 mg/min to help minimize the risk of infusion reactions *[see Dosage and Administration (2)]*.

5.3 Myelosuppression

Because of the potential for bone marrow suppression, careful hematologic monitoring is required during use of DOXIL, including white blood cell, neutrophil, platelet counts, and Hgb/Hct. With the recommended dosage schedule, leukopenia is usually transient. Hematologic toxicity may require dose reduction or delay or suspension of DOXIL therapy. Persistent severe myelosuppression may result in superinfection, neutropenic fever, or hemorrhage. Development of sepsis in the setting of neutropenia has resulted in discontinuation of treatment and, in rare cases, death.

DOXIL may potentiate the toxicity of other anticancer therapies. In particular, hematologic toxicity may be more severe when DOXIL is administered in combination with other agents that cause bone marrow suppression.

In patients with relapsed ovarian cancer, myelosuppression was generally moderate and reversible. In the three single-arm studies, anemia was the most common hematologic adverse reaction (52.6%), followed by leukopenia (WBC< 4,000 mm^3; 42.2%), thrombocytopenia (24.2%), and neutropenia (ANC <1,000; 19.0%). In the randomized study, anemia was the most common hematologic adverse reaction (40.2%), followed by leukopenia (WBC <4,000 mm^3; 36.8%), neutropenia (ANC <1,000; 35.1%), and thrombocytopenia (13.0%) *[see Adverse Reactions (6.2)]*.

In patients with relapsed ovarian cancer, 4.6% received G-CSF (or GM-CSF) to support their blood counts *[see Dosage and Administrations (2.5)]*.

For patients with AIDS-related Kaposi's sarcoma who often present with baseline myelosuppression due to such factors as their HIV disease or concomitant medications, myelosuppression appears to be the dose-limiting adverse reaction at the recommended dose of 20 mg/m^2 *[see Adverse Reactions (6.2)]*. Leukopenia is the most common adverse reaction experienced in this population; anemia and thrombocytopenia can also be expected. Sepsis occurred in 5% of patients; for 0.7% of patients the event was considered possibly or probably related to DOXIL. Eleven patients (1.6%) discontinued study because of bone marrow suppression or neutropenia.

Table 10 presents data on myelosuppression in patients with multiple myeloma receiving DOXIL and bortezomib in combination *[see Adverse Reactions (6.2)]*.

5.4 Hand-Foot Syndrome (HFS)

In the randomized ovarian cancer study, 50.6% of patients treated with DOXIL at 50 mg/m^2 every 4 weeks experienced HFS (developed palmar-plantar skin eruptions characterized by swelling, pain, erythema and, for some patients, desquamation of the skin on the hands and the feet), with 23.8% of the patients reporting HFS Grade 3 or 4 events. Ten subjects (4.2%) discontinued treatment due to HFS or other skin toxicity. HFS toxicity grades are described above *[see definitions of HFS grades in Dosage and Administration (2.5)]*.

Among 705 patients with AIDS-related Kaposi's sarcoma treated with DOXIL at 20 mg/m^2 every 2 weeks, 24 (3.4%) developed HFS, with 3 (0.9%) discontinuing.

In the randomized multiple myeloma study, 19% of patients treated with DOXIL at 30 mg/m^2 every three weeks experienced HFS.

HFS was generally observed after 2 or 3 cycles of treatment but may occur earlier. In most patients the reaction is mild and resolves in one to two weeks so that prolonged delay of therapy need not occur. However, dose modification may be required to manage HFS *[see Dosage and Administration (2.5)]*. The reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

5.5 Radiation Recall Reaction

Recall reaction has occurred with DOXIL administration after radiotherapy.

5.6 Fetal Mortality

Pregnancy Category D

DOXIL can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If DOXIL is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. If pregnancy occurs in the first few months following treatment with DOXIL, the prolonged half-life of the drug must be considered. Women of childbearing potential should be advised to avoid pregnancy during treatment with Doxil. *[see Use in Specific Populations (8.1)]*.

5.7 Toxicity Potentiation

The doxorubicin in DOXIL may potentiate the toxicity of other anticancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with the conventional formulation of doxorubicin HCl. Radiation-induced toxicity to the myocardium, mucosae, skin, and liver have been reported to be increased by the administration of doxorubicin HCl.

5.8 Monitoring: Laboratory Tests

Complete blood counts, including platelet counts, should be obtained frequently and at a minimum prior to each dose of DOXIL *[see Warnings and Precautions (5.3)]*.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reactions Profile

The following adverse reactions are discussed in more detail in other sections of the labeling.

- Cardiac Toxicity *[see Warnings and Precautions (5.1)]*
- Infusion reactions *[see Warnings and Precautions (5.2)]*
- Myelosuppression *[see Warnings and Precautions (5.3)]*

- Hand-Foot syndrome *[see Warnings and Precautions (5.4)]*

The most common adverse reactions observed with DOXIL are asthenia, fatigue, fever, nausea, stomatitis, vomiting, diarrhea, constipation, anorexia, hand-foot syndrome, rash and neutropenia, thrombocytopenia and anemia.

The most common serious adverse reactions observed with DOXIL are described in Section 6.2.

The safety data described below reflect exposure to DOXIL in 1310 patients including: 239 patients with ovarian cancer, 753 patients with AIDS-related Kaposi's sarcoma and 318 patients with multiple myeloma *[see Adverse Reactions in Clinical Trials (6.2)]*.

6.2 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates on other clinical trials and may not reflect the rates observed in clinical practice.

The following tables present adverse reactions from clinical trials of DOXIL in ovarian cancer and AIDS-Related Kaposi's sarcoma.

Patients With Ovarian Cancer

The safety data described below are from 239 patients with ovarian cancer treated with DOXIL (doxorubicin HCl liposome injection) at 50 mg/m^2 once every 4 weeks for a minimum of 4 courses in a randomized, multicenter, open-label study. In this study, patients received DOXIL for a median number of 98.0 days (range 1-785 days). The population studied was 27-87 years of age, 91% Caucasian, 6% Black and 3% Hispanic and other.

Table 6 presents the hematologic adverse reactions from the randomized study of DOXIL compared to topotecan.

Table 6: Ovarian Cancer Randomized Study Hematology Data Reported in Patients With Ovarian Cancer

	DOXIL Patients (n = 239)	Topotecan Patients (n = 235)
Neutropenia		
500 - <1000/mm^3	19 (7.9%)	33 (14.0%)
<500/mm^3	10 (4.2%)	146 (62.1%)
Anemia		
6.5 - <8 g/dL	13 (5.4%)	59 (25.1%)
< 6.5 g/dL	1 (0.4%)	10 (4.3%)
Thrombocytopenia		
10,000 - <50,000/mm^3	3 (1.3%)	40 (17.0%)
<10,000/mm^3	0 (0.0%)	40 (17.0%)

Table 7 presents a comparative profile of the non-hematologic adverse reactions from the randomized study of DOXIL compared to topotecan.

Table 7: Ovarian Cancer Randomized Study

Non-Hematologic Adverse Reaction 10% or Greater	DOXIL (%) treated (n = 239)		Topotecan (%) treated (n =235)	
	All grades	Grades 3-4	All grades	Grades 3-4
Body as a Whole				
Asthenia	40.2	7.1	51.5	8.1
Fever	21.3	0.8	30.6	5.5
Mucous Membrane Disorder	14.2	3.8	3.4	0
Back Pain	11.7	1.7	10.2	0.9
Infection	11.7	2.1	6.4	0.9
Headache	10.5	0.8	14.9	0
Digestive				
Nausea	46.0	5.4	63.0	8.1
Stomatitis	41.4	8.3	15.3	0.4
Vomiting	32.6	7.9	43.8	9.8
Diarrhea	20.9	2.5	34.9	4.2
Anorexia	20.1	2.5	21.7	1.3
Dyspepsia	12.1	0.8	14.0	0
Nervous				
Dizziness	4.2	0	10.2	0
Respiratory				
Pharyngitis	15.9	0	17.9	0.4
Dyspnea	15.1	4.1	23.4	4.3
Cough increased	9.6	0	11.5	0
Skin and Appendages				
Hand-foot syndrome	50.6	23.8	0.9	0
Rash	28.5	4.2	12.3	0.4
Alopecia	19.2	N/A	52.3	N/A

The following additional adverse reactions (not in table) were observed in patients with ovarian cancer with doses administered every four weeks.

Incidence 1% to 10%

Cardiovascular: vasodilation, tachycardia, deep thrombophlebitis, hypotension, cardiac arrest.

Digestive: oral moniliasis, mouth ulceration, esophagitis, dysphagia, rectal bleeding, ileus.

Hemic and Lymphatic: ecchymosis.

Metabolic and Nutritional: dehydration, weight loss, hyperbilirubinemia, hypokalemia, hypercalcemia, hyponatremia.

Nervous: somnolence, dizziness, depression.

Respiratory: rhinitis, pneumonia, sinusitis, epistaxis.

Skin and Appendages: pruritus, skin discoloration, vesiculobullous rash, maculopapular rash, exfoliative dermatitis, herpes zoster, dry skin, herpes simplex, fungal dermatitis, furunculosis, acne.

Special Senses: conjunctivitis, taste perversion, dry eyes.

Urinary: urinary tract infection, hematuria, vaginal moniliasis.

Patients With AIDS-Related Kaposi's Sarcoma

The safety data below is based on the experience reported in 753 patients with AIDS-related Kaposi's sarcoma enrolled in four studies. The median age of the population was 38.7 years (range 24-70 years), which was 99% male, 1% female, 88% Caucasian, 6% Hispanic, 4% Black, and 2% Asian/other/unknown. The majority of patients were treated with 20 mg/m^2 of DOXIL every two to three weeks. The median time on study was 127 days and ranged from 1 to 811 days. The median cumulative dose was 120 mg/m^2 and ranged from 3.3 to 798.6 mg/m^2. Twenty-six patients (3.0%) received cumulative doses of greater than 450 mg/m^2.

Of these 753 patients, 61.2% were considered poor risk for KS tumor burden, 91.5% poor for immune system, and 46.9% for systemic illness; 36.2% were poor risk for all three categories. Patients' median CD4 count was 21.0 cells/mm^3, with 50.8% of patients having less than 50 cells/mm^3. The mean absolute neutrophil count at study entry was approximately 3,000 cells/mm^3.

Patients received a variety of potentially myelotoxic drugs in combination with DOXIL. Of the 693 patients with concomitant medication information, 58.7% were on one or more antiretroviral medications; 34.9% patients were on zidovudine (AZT), 20.8% on didanosine (ddI), 16.5% on zalcitabine (ddC), and 9.5% on stavudine (D4T). A total of 85.1% patients were

on PCP prophylaxis, most (54.4%) on sulfamethoxazole/trimethoprim. Eighty-five percent of patients were receiving antifungal medications, primarily fluconazole (75.8%). Seventy-two percent of patients were receiving antivirals, 56.3% acyclovir, 29% ganciclovir, and 16% foscarnet. In addition, 47.8% patients received colony-stimulating factors (sargramostim/filgrastim) sometime during their course of treatment.

Adverse reactions led to discontinuation of treatment in 5% of patients with AIDS related Kaposi's sarcoma. Those that did so included bone marrow suppression, cardiac adverse reactions, infusion-related reactions, toxoplasmosis, HFS, pneumonia, cough/dyspnea, fatigue, optic neuritis, progression of a non-KS tumor, allergy to penicillin, and unspecified reasons.

Table 8: Hematology Data Reported in Patients With AIDS-Related Kaposi's Sarcoma

	Patients With Refractory or Intolerant AIDS-Related Kaposi's Sarcoma (n = 74)		Total Patients With AIDS-Related Kaposi's Sarcoma (n = 720)	
Neutropenia				
< 1000/mm^3	34	(45.9%)	352	(48.9%)
< 500/mm^3	8	(10.8%)	96	(13.3%)
Anemia				
< 10 g/dL	43	(58.1%)	399	(55.4%)
< 8 g/dL	12	(16.2%)	131	(18.2%)
Thrombocytopenia				
< 150,000/mm^3	45	(60.8%)	439	(60.9%)
< 25,000/mm^3	1	(1.4%)	30	(4.2%)

Table 9: Probably and Possibly Drug-Related Non-Hematologic Adverse Reactions Reported in ≥ 5% of Patients With AIDS-Related Kaposi's Sarcoma

Adverse Reactions	Patients With Refractory or Intolerant AIDS-Related Kaposi's Sarcoma (n = 77)		Total Patients With AIDS-Related Kaposi's Sarcoma (n = 705)	
Nausea	14	(18.2%)	119	(16.9%)
Asthenia	5	(6.5%)	70	(9.9%)
Fever	6	(7.8%)	64	(9.1%)
Alopecia	7	(9.1%)	63	(8.9%)
Alkaline Phosphatase Increase	1	(1.3%)	55	(7.8%)
Vomiting	6	(7.8%)	55	(7.8%)
Diarrhea	4	(5.2%)	55	(7.8%)
Stomatitis	4	(5.2%)	48	(6.8%)
Oral Moniliasis	1	(1.3%)	39	(5.5%)

The following additional (not in table) adverse reactions were observed in patients with AIDS-related Kaposi's sarcoma.

Incidence 1% to 5%

Body as a Whole: headache, back pain, infection, allergic reaction, chills.

Cardiovascular: chest pain, hypotension, tachycardia.

Cutaneous: herpes simplex, rash, itching.

Digestive: mouth ulceration, anorexia, dysphagia.

Metabolic and Nutritional: SGPT increase, weight loss, hyperbilirubinemia.

Other: dyspnea, pneumonia, dizziness, somnolence.

Incidence Less Than 1%

Body As A Whole: sepsis, moniliasis, cryptococcosis.

Cardiovascular: thrombophlebitis, cardiomyopathy, palpitation, bundle branch block, congestive heart failure, heart arrest, thrombosis, ventricular arrhythmia.

Digestive: hepatitis.

Metabolic and Nutritional Disorders: dehydration

Respiratory: cough increase, pharyngitis.

Skin and Appendages: maculopapular rash, herpes zoster.

Special Senses: taste perversion, conjunctivitis.

Patients With Multiple Myeloma

The safety data below are from 318 patients treated with DOXIL (30 mg/m^2 as a 1-hr i.v. infusion) administered on day 4 following bortezomib (1.3 mg/m^2 i.v. bolus on days 1, 4 , 8 and 11) every three weeks, in a randomized, open-label, multicenter study. In this study, patients in the DOXIL + bortezomib combination group were treated for a median number of 138 days (range 21-410 days). The population was 28-85 years of age, 58% male, 42% female, 90% Caucasian, 6% Black, and 4% Asian and other. Table 10 lists adverse reactions reported in 10% or more of patients treated with DOXIL in combination with bortezomib for multiple myeloma.

Table 10. Frequency of treatment emergent adverse reactions reported in ≥10% patients treated for multiple myeloma with DOXIL in combination with bortezomib, by Severity, Body System, and MedDRA Terminology.

Adverse Reaction	DOXIL + bortezomib (n=318)			Bortezomib (n=318)		
	Any (%)	Grade 3	Grade 4	Any (%)	Grade 3	Grade 4
Blood and lymphatic system disorders						
Neutropenia	36	22	10	22	11	5
Thrombocytopenia	33	11	13	28	9	8
Anemia	25	7	2	21	8	2
General disorders and administration site conditions						
Fatigue	36	6	1	28	3	0
Pyrexia	31	1	0	22	1	0
Asthenia	22	6	0	18	4	0
Gastrointestinal disorders						
Nausea	48	3	0	40	1	0
Diarrhea	46	7	0	39	5	0
Vomiting	32	4	0	22	1	0

Continued

Adverse Reaction	DOXIL + bortezomib (n=318)			Bortezomib (n=318)		
	Any (%)	Grade 3	Grade 4	Any (%)	Grade 3	Grade 4
Constipation	31	1	0	31	1	0
Mucositis/Stomatitis	20	2	0	5	<1	0
Abdominal pain	11	1	0	8	1	0
Infections and infestations						
Herpes zoster	11	2	0	9	2	0
Herpes simplex	10	0	0	6	1	0
Investigations						
Weight decreased	12	0	0	4	0	0
Metabolism and Nutritional disorders						
Anorexia	19	2	0	14	<1	0
Nervous system disorders						
Peripheral Neuropathy*	42	7	<1	45	10	1
Neuralgia	17	3	0	20	4	1
Paresthesia/dysesthesia	13	<1	0	10	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	18	0	0	12	0	0
Skin and subcutaneous tissue disorders						
Rash**	22	1	0	18	1	0
Hand-foot syndrome	19	6	0	<1	0	0

*Peripheral neuropathy includes the following adverse reactions: peripheral sensory neuropathy, neuropathy peripheral, polyneuropathy, peripheral motor neuropathy, and neuropathy NOS.

**Rash includes the following adverse reactions: rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, exfoliative rash, and rash generalized.

6.3 Post Marketing Experience

The following additional adverse reactions have been identified during post approval use of DOXIL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Musculoskeletal and Connective Tissue Disorders: rare cases of muscle spasms.

Respiratory, Thoracic and Mediastinal Disorders: rare cases of pulmonary embolism (in some cases fatal).

Hematologic disorders: Secondary acute myelogenous leukemia with and without fatal outcome has been reported in patients whose treatment included DOXIL.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with DOXIL. DOXIL may interact with drugs known to interact with the conventional formulation of doxorubicin HCl.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.6)]*.

DOXIL is embryotoxic at doses of 1 mg/kg/day in rats and is embryotoxic and abortifacient at 0.5 mg/kg/day in rabbits (both doses are about one-eighth the 50 mg/m^2 human dose on a mg/m^2 basis). Embryotoxicity was characterized by increased embryo-fetal deaths and reduced live litter sizes.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs, including anthracyclines, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from DOXIL, mothers should discontinue nursing prior to taking this drug.

8.4 Pediatric Use

The safety and effectiveness of DOXIL in pediatric patients have not been established.

8.5 Geriatric Use

Of the patients treated with DOXIL in the randomized ovarian cancer study, 34.7% (n=83) were 65 years of age or older while 7.9% (n=19) were 75 years of age or older. Of the 318 patients treated with DOXIL in combination with bortezomib for multiple myeloma, 37% were 65 years of age or older and 8% were 75 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Hepatic Impairment

The pharmacokinetics of DOXIL has not been adequately evaluated in patients with hepatic impairment. Doxorubicin is eliminated in large part by the liver. Thus, DOXIL dosage should be reduced in patients with impaired hepatic function *[see Dosage and Administration (2.6)]*.

Prior to DOXIL administration, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase, and bilirubin *[see Dosage and Administration (2.6)]*.

10 OVERDOSAGE

Acute overdosage with doxorubicin HCl causes increases in mucositis, leucopenia, and thrombocytopenia.

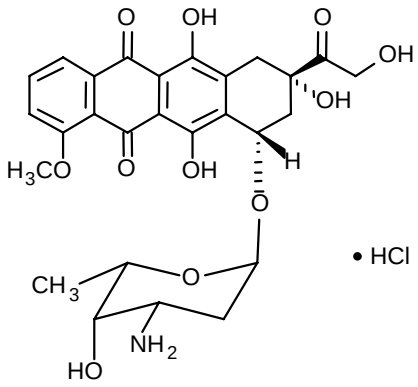
Treatment of acute overdosage consists of treatment of the severely myelosuppressed patient with hospitalization, antibiotics, platelet and granulocyte transfusions, and symptomatic treatment of mucositis.

11 DESCRIPTION

DOXIL (doxorubicin HCl liposome injection) is doxorubicin hydrochloride (HCl) encapsulated in STEALTH® liposomes for intravenous administration.

Doxorubicin is an anthracycline topoisomerase inhibitor isolated from *Streptomyces peucetius* var. *caesius*.

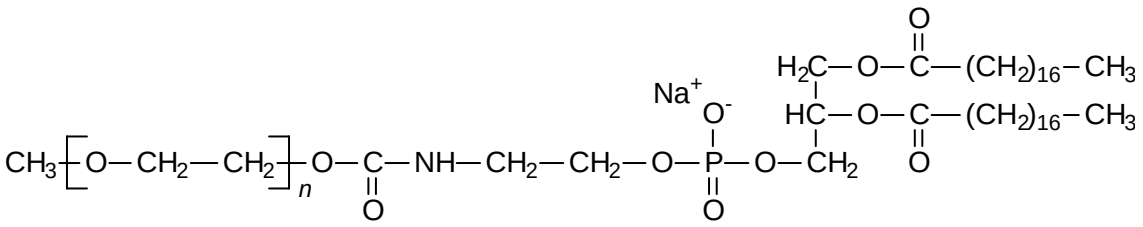
Doxorubicin HCl, which is the established name for (8S,10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride, has the following structure:



The molecular formula of the drug is C27 H29 NO11·HCl; its molecular weight is 579.99.

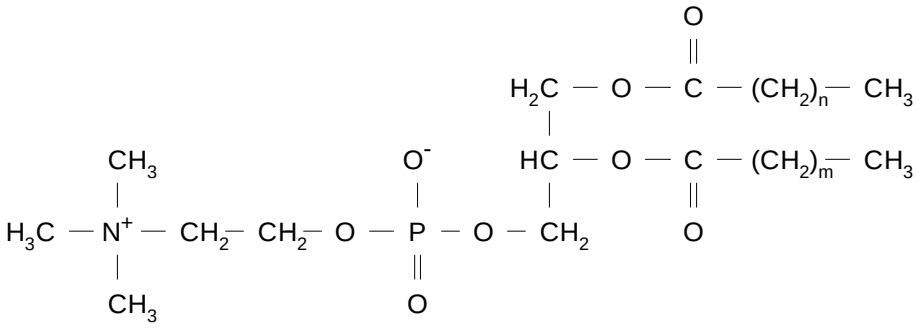
DOXIL is provided as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials. Each vial contains 20 mg or 50 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The STEALTH® liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the STEALTH® liposomes.

MPEG-DSPE has the following structural formula:



n = ca. 45

HSPC has the following structural formula:



m, n = 14 or 16

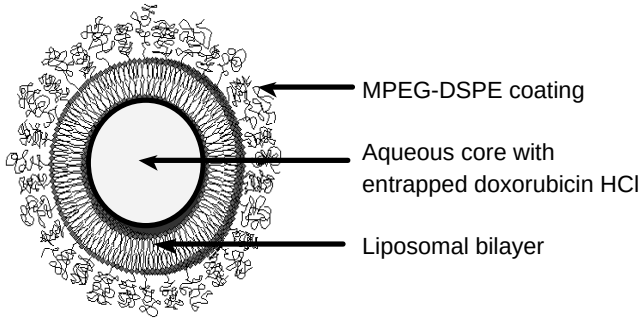
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The active ingredient of DOXIL is doxorubicin HCl. 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 is doxorubicin HCl encapsulated in long-circulating STEALTH® liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH® liposomes of DOXIL are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time.

Representation of a STEALTH® liposome:



STEALTH® liposomes have a half-life of approximately 55 hours in humans. They are stable in blood, and direct measurement of liposomal doxorubicin shows that at least 90% of the drug (the assay used cannot quantify less than 5-10% free doxorubicin) remains liposome-encapsulated during circulation.

It is hypothesized that because of their small size (ca. 100 nm) and persistence in the circulation, the pegylated DOXIL liposomes are able to penetrate the altered and often compromised vasculature of tumors. This hypothesis is supported by studies using colloidal gold-containing STEALTH® liposomes, which can be visualized microscopically. Evidence of penetration of STEALTH® liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C-26 colon carcinoma tumors and in transgenic mice with Kaposi's sarcoma-like lesions. Once the STEALTH® liposomes distribute to the tissue compartment, the encapsulated doxorubicin HCl becomes available. The exact mechanism of release is not understood.

12.3 Pharmacokinetics

The plasma pharmacokinetics of DOXIL were evaluated in 42 patients with AIDS-related Kaposi's sarcoma (KS) who received single doses of 10 or 20 mg/m^2 administered by a 30-minute infusion. Twenty-three of these patients received single doses of both 10 and 20 mg/m^2 with a 3-week wash-out period between doses. The pharmacokinetic parameter values of DOXIL, given for total doxorubicin (mostly liposomally bound), are presented in Table 11.

Table 11: Pharmacokinetic Parameters of DOXIL in Patients With AIDS-Related Kaposi's Sarcoma

	Dose	
Parameter (units)	10 mg/m^2	20 mg/m^2
Peak Plasma Concentration (μg/mL)	4.12 ± 0.215	8.34 ± 0.49
Plasma Clearance (L/h/m^2)	0.056 ± 0.01	0.041 ± 0.004
Steady State Volume of Distribution (L/m^2)	2.83 ± 0.145	2.72 ± 0.120
AUC (μg/mL•h)	277 ± 32.9	590 ± 58.7
First Phase (λ_1) Half-Life (h)	4.7 ± 1.1	5.2 ± 1.4
Second Phase (λ_1) Half-Life (h)	52.3 ± 5.6	55.0 ± 4.8

N = 23
Mean ± Standard Error

DOXIL displayed linear pharmacokinetics over the range of 10 to 20 mg/m^2. Disposition occurred in two phases after DOXIL administration, with a relatively short first phase (≈ 5 hours) and a prolonged second phase (≈ 55 hours) that accounted for the majority of the area under the curve (AUC).

The pharmacokinetics of DOXIL at a 50 mg/m^2 dose is reported to be nonlinear. At this dose, the elimination half-life of DOXIL is expected to be longer and the clearance lower compared to a 20 mg/m^2 dose. The exposure (AUC) is thus expected to be more than proportional at a 50 mg/m^2 dose when compared with the lower doses.

Distribution:

In contrast to the pharmacokinetics of doxorubicin, which displays a large volume of distribution, ranging from 700 to 1100 L/m^2, the small steady state volume of distribution of DOXIL shows that DOXIL is confined mostly to the vascular fluid volume. Plasma protein binding of DOXIL has not been determined; the plasma protein binding of doxorubicin is approximately 70%.

Metabolism:

Doxorubicinol, the major metabolite of doxorubicin, was detected at very low levels (range: of 0.8 to 26.2 ng/mL) in the plasma of patients who received 10 or 20 mg/m^2 DOXIL.

Excretion:

The plasma clearance of DOXIL was slow, with a mean clearance value of 0.041 L/h/m^2 at a dose of 20 mg/m^2. This is in contrast to doxorubicin, which displays a plasma clearance value ranging from 24 to 35 L/h/m^2.

Because of its slower clearance, the AUC of DOXIL, primarily representing the circulation of liposome-encapsulated doxorubicin, is approximately two to three orders of magnitude larger than the AUC for a similar dose of conventional doxorubicin HCl as reported in the literature.

Special Populations:

The pharmacokinetics of DOXIL have not been separately evaluated in women, in members of different ethnic groups, or in individuals with renal or hepatic insufficiency.

Drug-Drug Interactions:

Drug-drug interactions between DOXIL and other drugs, including antiviral agents, have not been adequately evaluated in patients with ovarian cancer, AIDS-related Kaposi's sarcoma or multiple myeloma.

Tissue Distribution in Patients with Kaposi's Sarcoma:

Kaposi's sarcoma lesions and normal skin biopsies were obtained at 48 and 96 hours post infusion of 20 mg/m^2 DOXIL in 11 patients. The concentration of DOXIL in KS lesions was a median of 19 (range, 3-53) times higher than in normal skin at 48 hours post treatment; however, this was not corrected for likely differences in blood content between KS lesions and normal skin. The corrected ratio may lie between 1 and 22 times. Thus, higher concentrations of DOXIL are delivered to KS lesions than to normal skin.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Although no studies have been conducted with DOXIL, doxorubicin HCl and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models.

STEALTH® liposomes without drug were negative when tested in Ames, mouse lymphoma and chromosomal aberration assays *in vitro*, and mammalian micronucleus assay *in vivo*.

The possible adverse effects on fertility in males and females in humans or experimental animals have not been adequately evaluated. However, DOXIL resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 mg/kg (about twice the 50 mg/m^2 human dose on a mg/m^2 basis). Decreased testicular weights and hypospermia were present in rats after repeat doses ≥ 0.25 mg/kg/day (about one thirtieth the 50 mg/m^2 human dose on a mg/m^2 basis), and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis were observed in dogs after repeat doses of 1 mg/kg/day (about one half the 50 mg/m^2 human dose on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Ovarian Cancer

DOXIL (doxorubicin HCl liposome injection) was studied in three open-label, single-arm, clinical studies of 176 patients with metastatic ovarian cancer. One hundred forty-five (145) of these patients were refractory to both paclitaxel- and platinum-based chemotherapy regimens.

Refractory ovarian cancer is defined as disease progression while on treatment, or relapse within 6 months of completing treatment. Patients in these studies received DOXIL at 50 mg/m^2 infused over one hour every 3 or 4 weeks for 3-6 cycles or longer in the absence of dose-limiting toxicity or progression of disease.

The baseline demographics and clinical characteristics of the patients with refractory ovarian cancer are provided in **Table 12** below.

Table 12: Patient Demographics for Patients With Refractory Ovarian Cancer From Single Arm Ovarian Cancer Studies

	Study 1 (U.S.) (n = 27)	Study 2 (U.S.) (n = 82)	Study 3 (non-U.S.) (n = 36)
Age at Diagnosis (Years)			
Median	64	61.5	51.5
Range	46 – 75	34 – 85	22 – 80
Drug-Free Interval (Months)			
Median	1.8	1.7	2.6
Range	0.5 – 15.6	0.6 – 7.0	0.7 – 15.2
Sum of Lesions at Baseline (cm^2)			
Median	25	18.3	32.4
Range	1.2 – 230.0	1.3 – 285.0	0.3 – 114.0
FIGO Staging			
I	1 (3.7%)	3 (3.7%)	4 (11.1%)
II	3 (11.1%)	3 (3.7%)	1 (2.8%)
III	15 (55.6%)	60 (73.2%)	24 (66.7%)
IV	8 (29.6%)	16 (19.5%)	6 (16.7%)
Not Specified	—	—	1 (2.8%)
CA-125 at Baseline			
Median	123.5	199.0	1004.5
Range	20 – 14,012	7 – 46,594	20 – 12,089
Number of Prior Chemotherapy Regimens			
1	7 (25.9%)	13 (15.9%)	9 (25.0%)
2	11 (40.7%)	44 (53.7%)	19 (52.8%)
3	6 (22.2%)	25 (30.5%)	8 (22.8%)
4	3 (11.1%)	—	—

The primary efficacy parameter was response rate for the population of patients refractory to both paclitaxel- and a platinum-containing regimen. Assessment of response was based on Southwest Oncology Group (SWOG) criteria, and required confirmation four weeks after the initial observation. Secondary efficacy parameters were time to response, duration of response, and time to progression.

The response rates for the individual single arm studies are given in **Table 13** below.

Table 13: Response Rates in Patients With Refractory Ovarian Cancer From Single Arm Ovarian Cancer Studies

	Study 1 (U.S.)	Study 2 (U.S.)	Study 3 (non-U.S.)
Response Rate	22.2% (6/27)	17.1% (14/82)	0% (0/36)
95% Confidence Interval	8.6% - 42.3%	9.7% - 27.0%	0.0% - 9.7%

When the data from the single arm studies are combined, the response rate for all patients refractory to paclitaxel and platinum agents was 13.8% (20/145) (95% CI 8.1% to 19.3%). The median time to progression was 15.9 weeks, the median time to response was 17.6 weeks, and the duration of response was 39.4 weeks.

DOXIL (doxorubicin HCl liposome injection) was also studied in a randomized, multicenter, open-label, study in 474 patients with epithelial ovarian cancer after platinum-based chemotherapy. Patients in this study received an initial dose of either DOXIL 50 mg/m^2 infused over one hour every 4 weeks or topotecan 1.5 mg/m^2 infused daily for 5 consecutive days every 3 weeks. Patients were stratified according to platinum sensitivity and the presence of bulky disease (presence of tumor mass greater than 5 cm in size). Platinum sensitivity is defined by response to initial platinum-based therapy and a progression-free interval of greater than 6 months off treatment. The primary efficacy endpoint for this study was time to progression (TTP). Other efficacy endpoints included overall survival and objective response rate.

The baseline patient demographic and clinical characteristics are provided in **Table 14** below.

Table 14: Ovarian Cancer Randomized Study Baseline Demographic and Clinical Characteristics

	DOXIL (n = 239)	Topotecan (n = 235)
Age at Diagnosis (Years)		
Median	60.0	60.0
Range	27 – 87	25 – 85
Drug-Free Interval (Months)		
Median	7.0	6.7
Range	0.9 – 82.1	0.5 – 109.6
FIGO Staging		
I	11 (4.6%)	15 (6.4%)
II	13 (5.4%)	8 (3.4%)
III	175 (73.2%)	164 (69.8%)
IV	40 (16.7%)	48 (20.4%)
Platinum Sensitivity		
Sensitive	109 (45.6%)	110 (46.8%)
Refractory	130 (54.4%)	125 (53.2%)
Bulky Disease		
Present	108 (45.2%)	105 (44.7%)
Absent	131 (54.8%)	130 (55.3%)

Study results are provided in **Table 15**.

There was no statistically significant difference in TTP between the two treatment arms.

Table 15: Results of Efficacy Analyses[a]

	Protocol Defined ITT Population	
	DOXIL (n = 239)	Topotecan (n = 235)
TTP (Protocol Specified Primary Endpoint)		
Median (Months)[b]	4.1	4.2
p-value[c]	0.617	
Hazard Ratio[d]	0.955	
95% CI for Hazard Ratio	(0.762, 1.196)	
Overall Survival		
Median (Months) [b]	14.4	13.7
p-value*	0.05	
Hazard Ratio[d]	0.822	
95% CI for Hazard Ratio	(0.676, 1.000)	
Response Rate		
Overall Response n (%)	47 (19.7)	40 (17.0)
Complete Response n (%)	9 (3.8)	11 (4.7)
Partial Response n (%)	38 (15.9)	29 (12.3)
Median Duration of Response (Months) [b]	6.9	5.9

[a] Analysis based on investigators' strata for protocol defined ITT population.
[b] Kaplan-Meier estimates.
[c] p-value is based on the stratified log-rank test.
[d] Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than 1 indicates an advantage for DOXIL.
* p-value not adjusted for multiple comparisons.

14.2 AIDS-Related Kaposi's Sarcoma

DOXIL was studied in an open-label, single-arm, multicenter study utilizing DOXIL at 20 mg/m^2 by intravenous infusion every three weeks, generally until progression or intolerance occurred. In an interim analysis, the treatment history of 383 patients was reviewed, and a cohort of 77 patients was retrospectively identified as having disease progression on prior systemic combination chemotherapy (at least 2 cycles of a regimen containing at least two of three treatments: bleomycin, vincristine or vinblastine, or doxorubicin) or as being intolerant to such therapy. Forty-nine of the 77 (64%) patients had received prior doxorubicin HCl.

These 77 patients were predominantly Caucasian, homosexual males with a median CD4 count of 10 cells/mm^3. Their age ranged from 24 to 54 years, with a mean age of 38 years. Using the ACTG staging criteria, 78% of the patients were at poor risk for tumor burden, 96% at poor risk for immune system, and 58% at poor risk for systemic illness at baseline. Their mean Karnofsky status score was 74%. All 77 patients had cutaneous or subcutaneous lesions, 40% also had oral lesions, 26% pulmonary lesions, and 14% of patients had lesions of the stomach/intestine.

The majority of these patients had disease progression on prior systemic combination chemotherapy.

The median time on study for these 77 patients was 155 days and ranged from 1 to 456 days. The median cumulative dose was 154 mg/m^2 and ranged from 20 to 620 mg/m^2.

Two analyses of tumor response were used to evaluate the effectiveness of DOXIL: one analysis based on investigator assessment of changes in lesions over the entire body, and one analysis based on changes in indicator lesions.

Investigator Assessment

Investigator response was based on modified ACTG criteria. Partial response was defined as no new lesions, sites of disease, or worsening edema; flattening of ≥50% of previously raised lesions or area of indicator lesions decreasing by ≥50%; and response lasting at least 21 days with no prior progression.

Indicator Lesion Assessment

A retrospectively defined analysis was conducted based on assessment of the response of up to five prospectively identified representative indicator lesions. A partial response was defined as flattening of ≥50% of previously raised indicator lesions, or >50% decrease in the area of indicator lesions and lasting at least 21 days with no prior progression.

Only patients with adequate documentation of baseline status and follow-up assessments were considered evaluable for response. Patients who received concomitant KS treatment during study, who completed local radiotherapy to sites encompassing one or more of the indicator lesions within two months of study entry, who had less than four indicator lesions, or who had less than three raised indicator lesions at baseline (the latter applies solely to indicator lesion assessment) were considered nonevaluable for response. Of the 77 patients who had disease progression on prior systemic combination chemotherapy or who were intolerant to such therapy, 34 were evaluable for investigator assessment and 42 were evaluable for indicator lesion assessment.

Table 16: Response in Patients with Refractory[a] AIDS-related Kaposi's Sarcoma

Investigator Assessment	All Evaluable Patients (n = 34)	Evaluable Patients Who Received Prior Doxorubicin (n = 20)
Response[b]		
Partial (PR)	27%	30%
Stable	29%	40%
Progression	44%	30%
Duration of PR (Days)		
Median	73	89
Range	42+ - 210+	42+ - 210+
Time to PR (Days)		
Median	43	53
Range	15 – 133	15 – 109

Indicator Lesion Assessment	All Evaluable Patients (n = 42)	Evaluable Patients Who Received Prior Doxorubicin (n = 23)
Response[b]		
Partial (PR)	48%	52%
Stable	26%	30%
Progression	26%	17%
Duration of PR (Days)		
Median	71	79
Range	22+ - 210+	35 - 210+
Time to PR (Days)		
Median	22	48
Range	15 – 109	15 – 109

[a] Patients with disease that progressed on prior combination chemotherapy or who were intolerant to such therapy.
[b] There were no complete responses in this population.

14.3 Multiple Myeloma

The safety and efficacy of DOXIL in combination with bortezomib in the treatment of multiple myeloma were evaluated in a randomized, open label, international multicenter study. This study included 646 patients who have not previously received bortezomib and whose disease progressed during or after at least one prior therapy. Patients were randomized (1:1 ratio) to receive either DOXIL (30 mg/m^2 as a 1-hr i.v. infusion) administered on day 4 following bortezomib (1.3 mg/m^2 i.v. bolus on days 1, 4 , 8 and 11) or bortezomib alone (1.3 mg/m^2 i.v. bolus on days 1, 4 , 8 and 11). Treatment was administered every 3 weeks. Patients were treated for up to 8 cycles until disease progression or the occurrence of unacceptable toxicity. Patients who maintained a response were allowed to receive further treatment. The median number of cycles in each treatment arm was 5 (range 1-18). The baseline demographics and clinical characteristics of the patients with multiple myeloma are provided in **Table 17** below.

Table 17 Summary of Baseline Patient and Disease Characteristics

Patient Characteristics	DOXIL + bortezomib n=324	bortezomib n=322
Median age in years (range)	61 (28, 85)	62 (34, 88)
% Male/female	58 / 42	54 / 46
% Caucasian/Black/other	90 / 6/ 4	94 / 4 / 2%
Disease Characteristics		
% with IgG/IgA/Light chain	57 / 27 / 12	62 / 24 /11
% β_2-microglobulin group		
≤2.5 mg/L	14	14
>2.5 mg/L and ≤5.5 mg/L	56	55
>5.5 mg/L	30	31
Serum M-protein (g/dL): Median (Range)	2.5 (0-10.0)	2.7 (0-10.0)
Urine M-protein (mg/24 hours): Median (Range)	107 (0-24883)	66 (0-39657)
Median Months Since Diagnosis	35.2	37.5
% Prior Therapy		
One	34	34
More than one	66	66
Prior Systemic Therapies for Multiple Myeloma		
Corticosteroid (%)	99	>99
Anthracyclines	68	67
Alkylating agent (%)	92	90
Thalidomide/lenalidomide (%)	40	43
Stem cell transplantation (%)	57	54

The primary endpoint in this study was time to progression (TTP). TTP was defined as the time from randomization to the first occurrence of progressive disease or death due to progressive disease. The combination arm demonstrated significant improvement in TTP. As the prespecified primary objective was achieved at the interim analysis, patients in the bortezomib monotherapy group were then allowed to receive the DOXIL + bortezomib combination. Survival continued to be followed after the interim analysis and survival data are not mature at this time. Efficacy results are as shown in **Table 18 and Figure 1.**

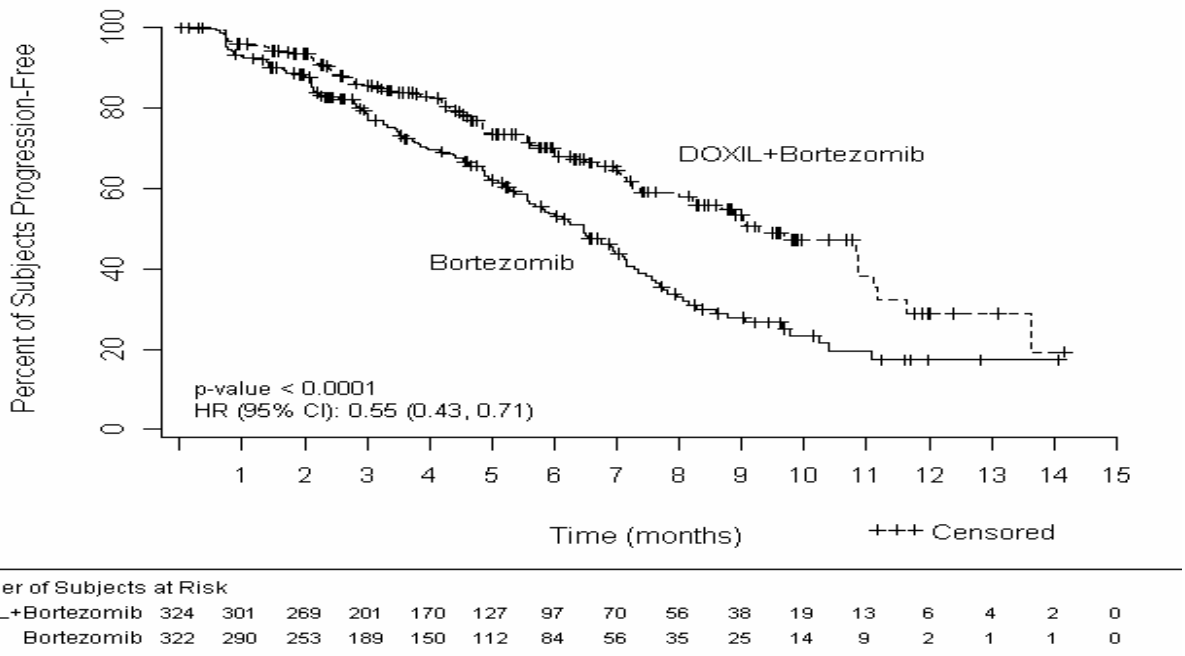
Table 18 Efficacy of DOXIL in combination with bortezomib in the treatment of patients with multiple myeloma

Endpoint	DOXIL + bortezomib n=324		Bortezomib n=322
Time to Progression[a]			
Progression or death due to progression (n)	99		150
Censored (n)	225		172
Median in days (months)	282 (9.3)		197 (6.5)
95% CI	250;338		170;217
Hazard ratio[b]		0.55	
(95% CI)		(0.43, 0.71)	
p-value[c]		<0.0001	
Response (n)[d]	303		310
% Complete Response (CR)	5		3
%Partial Response (PR)	43		40
%CR + PR	48		43
p-value[e]		0.251	
Median Duration of Response (months)	10.2		7.0
(95% CI)	(10.2;12.9)		(5.9;8.3)

[a] Kaplan Meier estimate.
[b] Hazard ratio based on stratified Cox proportional hazards regression. A hazard ratio < 1 indicates an advantage for DOXIL+bortezomib.
[c] Stratified log-rank test.
[d] RR as per EBMT criteria.
[e] Cochran-Mantel-Haenszel test adjusted for the stratification factors.

Time to progression outcomes were consistent with the overall result across most subgroups defined by patient demographic and baseline characteristics. There were too few Blacks or Asian patients to adequately assess differences in effects for the race subgroup.

Figure 1- Time to Progression Kaplan-Meier Curve



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16 HOW SUPPLIED/STORAGE AND HANDLING

DOXIL (doxorubicin HCl liposome injection) is supplied as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials.

Each 10-mL vial contains 20 mg doxorubicin HCl at a concentration of 2 mg/mL.

Each 30-mL vial contains 50 mg doxorubicin HCl at a concentration of 2 mg/mL.

Refrigerate unopened vials of DOXIL at 2°-8°C (36°-46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on DOXIL.

The following packages of six individually cartoned vials are available:

Table 19

mg in vial	fill volume	vial size	NDC #s
20 mg vial	10-mL	10-mL	17314-9600-1
50 mg vial	25-mL	30-mL	17314-9600-2

17 PATIENT COUNSELING INFORMATION

Patients and patients' caregivers should be informed of the expected adverse effects of DOXIL, particularly hand-foot syndrome, stomatitis, and neutropenia and related complications of neutropenic fever, infection, and sepsis.

Hand-Foot Syndrome (HFS): Patients who experience tingling or burning, redness, flaking, bothersome swelling, small blisters, or small sores on the palms of their hands or soles of their feet (symptoms of Hand-Foot Syndrome) should notify their physician.

Stomatitis: Patients who experience painful redness, swelling, or sores in the mouth (symptoms of stomatitis) should notify their physician.

Fever and Neutropenia: Patients who develop a fever of 100.5°F or higher should notify their physician.

Nausea, vomiting, tiredness, weakness, rash, or mild hair loss: Patients who develop any of these symptoms should notify their physician.

Following its administration, DOXIL may impart a reddish-orange color to the urine and other body fluids. This nontoxic reaction is due to the color of the product and will dissipate as the drug is eliminated from the body.

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

Distributed by:

Ortho Biotech Products, LP Raritan, NJ 08869-0670

{Package Eng.: To Add OBI Logo Here}

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