Product Information

DOXIL®

[däk'sil]

(doxorubicin HCl liposome injection)

FOR INTRAVENOUS INFUSION ONLY

WARNINGS

1. Myocardial damage may lead to congestive heart failure and may be encountered as the total cumulative dose of doxorubicin HCl approaches 550 mg/m^2. The use of DOXIL® (doxorubicin HCl liposome injection) may lead to cardiac toxicity. In a large 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 – Cardiac Toxicity**).
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–Infusion Reactions)**.
3. Severe myelosuppression may occur (see **WARNINGS–Myelosuppression**).
4. Dosage should be reduced in patients with impaired hepatic function (see **DOSAGE AND ADMINISTRATION**).
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 **DESCRIPTION** and **DOSAGE AND ADMINISTRATION**).
6. DOXIL® should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

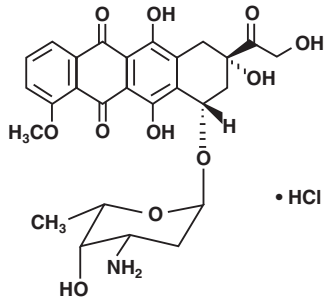
DESCRIPTION

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

Note: Liposomal encapsulation can substantially affect a drug's functional properties relative to those of the unencapsulated drug. In addition, different liposomal drug products may vary from one another in the chemical composition and physical form of the liposomes. Such differences can substantially affect the functional properties of liposomal drug products. DO NOT SUBSTITUTE.

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius* var. *caesius*.

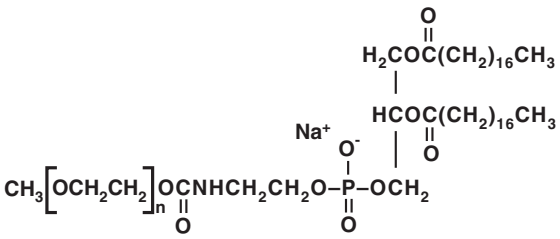
Doxorubicin HCl, which is the established name for (8*S*,10*S*)-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride, has the following structure:



The molecular formula of the drug is C_{27} H_{29} NO_{11}·HCl; its molecular weight is 579.99.

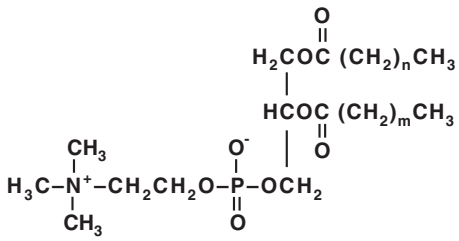
DOXIL® is provided as a sterile, translucent, red liposomal dispersion in 10-mL or 30-mL glass, single use vials. Each vial contains 20 mg or 50 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The STEALTH® liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine 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

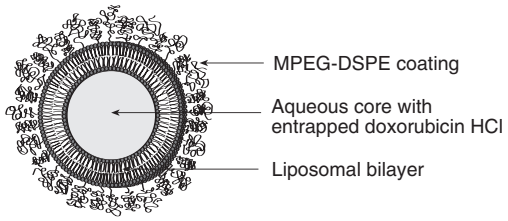
CLINICAL PHARMACOLOGY

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.

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 1**.

Table 1: 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 (λ1) Half-Life (h)	4.7 ± 1.1	5.2 ± 1.4
Second Phase (λ2) 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:

Although the patient populations for the current indications are on various medications, drug-drug interactions between DOXIL® and other drugs, including antiviral agents, have not been evaluated.

Tissue Distribution

Kaposi's sarcoma lesions and normal skin biopsies were obtained at 48 and 96 hours postinfusion 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 posttreatment; 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.

Clinical Studies

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 2** below.

Table 2: 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 study are given in **Table 3** below.

Table 3: 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 study 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 4** below.

Table 4: 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 5**.

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

Table 5: 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.

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 white, 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.

Responses are summarized in **Table 6**.

Table 6: 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.

INDICATIONS AND USAGE

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.

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.

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®.

DOXIL® IS CONTRAINDICATED IN NURSING MOTHERS.

WARNINGS

Cardiac Toxicity

Special attention must be given to the myocardial damage that may be associated with 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.

Caution should be observed in patients who have received other anthracyclines, and the total dose of doxorubicin HCl given should take into account any previous or concomitant therapy with other anthracyclines or related compounds. 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 (see **ADVERSE REACTIONS; cardiac events**).

In a large 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 (see also **BOX WARNING**).

Table 7: 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

Prior use of other anthracyclines or anthracenodiones 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.

Myelosuppression

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 event (52.6%), followed by leukopenia (WBC < 4000 mm^3; 42.2%), thrombocytopenia (24.2%), and neutropenia [ANC < 1000] (19.0%). In the randomized study, anemia was the most common hematologic adverse event (40.2%), followed by leukopenia (WBC < 4000 mm^3; 36.8%), neutropenia [ANC < 1000] (35.1%), and thrombocytopenia (13.0%) (see Hematology Data table in **ADVERSE REACTIONS, Ovarian Cancer Patients**).

In patients with relapsed ovarian cancer, 4.6% received G-CSF (or GM-CSF) to support their blood counts (see **DOSAGE AND ADMINISTRATION, Dose Modification Guidelines**).

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 event at the recommended dose of 20 mg/m^2 (see Hematology Data table in **ADVERSE REACTIONS, AIDS-Related Kaposi's Sarcoma Patients**). Leukopenia is the most common adverse event 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.

In all patients, 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.

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 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**).

Hand-Foot Syndrome (HFS)

In the randomized 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 (see definitions of HFS grades in **DOSAGE AND ADMINISTRATION, Dose Modification Guidelines**).

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

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, Dose Modification Guidelines**). The reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

Pregnancy Category D

DOXIL® can cause fetal harm when administered to a pregnant woman. 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.

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.

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.

Injection Site Effects

DOXIL® is not a vesicant, but 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 (see **DOSAGE AND ADMINISTRATION**). 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. **DOXIL® must not be given by the intramuscular or subcutaneous route**.

In studies with rabbits, lesions that were induced by subcutaneous injection of DOXIL® were minor and reversible compared to more severe and irreversible lesions and tissue necrosis that were induced after subcutaneous injection of conventional doxorubicin HCl.

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**).

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**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Secondary acute myelogenous leukemia has been reported in patients treated with topoisomerase II inhibitors, including anthracyclines.

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).

PRECAUTIONS

General

Patients receiving therapy with DOXIL® should be monitored by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse events are manageable with dose reductions or delays (see **DOSAGE AND ADMINISTRATION, Dose Modification Guidelines**).

Laboratory Tests

Complete blood counts, including platelet counts, should be obtained frequently and at a minimum prior to each dose of DOXIL®.

Drug Interactions

No formal drug interaction studies have been conducted with DOXIL®. Until specific compatibility data are available, it is not recommended that DOXIL® be mixed with other drugs. DOXIL® may interact with drugs known to interact with the conventional formulation of doxorubicin HCl.

Pregnancy

Pregnancy Category D (see **WARNINGS**).

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.

Pediatric Use

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

Geriatric Use

Of the 373 ovarian cancer patients treated in the single-arm studies, 29% were 60 to 69 years old, while 22.8% were 70 years old or older. Of the patients treated with DOXIL® in the randomized ovarian cancer study, 34.7% (n=83) were 65 years of age or older.

Radiation Therapy

Recall of a skin reaction due to prior radiotherapy has occurred with DOXIL® administration.

Information for the Patient

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.

ADVERSE REACTIONS

Patients With Ovarian Cancer

Safety data are available from 239 patients treated with DOXIL® (doxorubicin HCl liposome injection) on the randomized ovarian cancer study.

Table 8 presents the hematologic adverse events from the randomized study of DOXIL® compared to topotecan.

Table 8: 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 9 presents a comparative profile of the non-hematologic events from the randomized study of DOXIL® compared to topotecan.

Table 9: Ovarian Cancer Randomized Study

Non-Hematologic Adverse Event 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
Abdominal Pain	33.5	10.4	37.9	9.8
Fever	21.3	0.8	30.6	5.5
Pain	20.9	2.1	17.0	1.7
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
Constipation	30.1	2.5	45.5	5.6
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
Intestinal Obstruction	11.3	9.6	11.1	9.0
Metabolic/Nutritional Disorders				
Peripheral Edema	11.3	2.1	17.4	2.6
Nervous				
Paresthesia	10.0	0	8.9	0
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 events (not in table) were observed in patients with ovarian cancer with doses administered every four weeks; only events considered at least possibly drug-related by investigators are included.

Incidence 1% to 10%

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

Digestive: oral moniliasis, mouth ulceration, dry mouth, gingivitis, esophagitis, dysphagia, flatulence, rectal bleeding, ileus, abdomen enlarged, ascites.

Hemic and Lymphatic: ecchymosis.

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

Musculo-Skeletal: myalgia, arthralgia, pathological fracture.

Nervous: somnolence, dizziness, depression, insomnia, anxiety, confusion, neuropathy, hypertonia, agitation, neuralgia, peripheral neuritis, vertigo.

Respiratory: rhinitis, pneumonia, pleural effusion, sinusitis, apnea, epistaxis.

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

Special Senses: conjunctivitis, taste perversion, dry eyes, ear pain.

Urinary: urinary tract infection, dysuria, leukorrhea, urinary frequency, cystitis, hematuria, urinary incontinence, urinary urgency, vaginal moniliasis, vaginal bleeding, pelvic pain.

Patients With AIDS-Related Kaposi's Sarcoma

Information on adverse events is based on the experience reported in 753 patients with AIDS-related Kaposi's sarcoma enrolled in four studies. 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 3000 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.

Of the 753 patients enrolled in the DOXIL® clinical trials, adverse event information was available for 705 patients. In many instances, it was difficult to determine whether adverse events resulted from DOXIL®, from concomitant therapy, or from the patients' underlying disease(s).

Eighty-three percent of the patients reported adverse events that were considered to be possibly or probably related to the treatment with DOXIL®.

Adverse reactions only infrequently (5%) led to discontinuation of treatment. Those that did so included bone marrow suppression, cardiac adverse events, infusion-related reactions, toxoplasmosis, HFS, pneumonia, cough/dyspnea, fatigue, optic neuritis, progression of a non-KS tumor, allergy to penicillin, and unspecified reasons.

Table 10: 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 11: Probably and Possibly Drug-Related Non-Hematologic Adverse Events Reported in ≥5% of Patients With AIDS-Related Kaposi's Sarcoma

Adverse Event	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%)
Hypochromic Anemia	4	(5.2%)	69	(9.8%)
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 events were observed in patients with AIDS-related Kaposi's sarcoma; only events considered at least possibly drug-related by investigators are included.

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, glossitis, constipation, aphthous stomatitis, anorexia, dysphagia, abdominal pain.

Hematologic: hemolysis, increased prothrombin time.

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

Other: dyspnea, albuminuria, pneumonia, retinitis, emotional lability, dizziness, somnolence.

Incidence Less Than 1%

Body As A Whole: face edema, cellulitis, sepsis, abscess, radiation injury, flu syndrome, moniliasis, hypothermia, injection site hemorrhage, injection site pain, cryptococcosis, ascites.

Cardiovascular: thrombophlebitis, cardiomyopathy, pericardial effusion, hemorrhage, palpitation, syncope, bundle branch block, congestive heart failure, cardiomegaly, heart arrest, migraine, thrombosis, ventricular arrhythmia.

Digestive: dyspepsia, cholestatic jaundice, gastritis, gingivitis, ulcerative proctitis, colitis, esophageal ulcer, esophagitis, gastrointestinal hemorrhage, hepatic failure, leukoplakia of mouth, pancreatitis, ulcerative stomatitis, hepatitis, hepatosplenomegaly, increased appetite, jaundice, sclerosing cholangitis, tenesmus, fecal impaction.

Endocrine: diabetes mellitus.

Hemic and Lymphatic: eosinophilia, lymphadenopathy, lymphangitis, lymphedema, petechia, thromboplastin decrease.

Metabolic and Nutritional Disorders: lactic dehydrogenase increase, hypernatremia, creatinine increase, BUN increase, dehydration, edema, hypercalcemia, hyperkalemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hypolipemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypoproteinemia, ketosis, weight gain.

Musculo-Skeletal: myalgia, arthralgia, bone pain, myositis.

Nervous: paresthesia, insomnia, peripheral neuritis, depression, neuropathy, anxiety, convulsion, hypotonia, acute brain syndrome, confusion, hemiplegia, hypertonia, hypokinesia, vertigo.

Respiratory: pleural effusion, asthma, bronchitis, cough increase, hyperventilation, pharyngitis, pneumothorax, rhinitis, sinusitis.

Skin and Appendages: maculopapular rash, skin ulcer, skin discoloration, herpes zoster, exfoliative dermatitis, cutaneous moniliasis, erythema multiforme, erythema nodosum, furunculosis, psoriasis, pustular rash, skin necrosis, urticaria, vesiculobullous rash.

Special Senses: otitis media, taste perversion, abnormal vision, blindness, conjunctivitis, eye pain, optic neuritis, tinnitus, visual field defect.

Urogenital: hematuria, balanitis, cystitis, dysuria, genital edema, glycosuria, kidney failure.

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.

DOSAGE AND ADMINISTRATION

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 AEs 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 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 events such as HFS, stomatitis, or hematologic toxicity the doses may be delayed or reduced (see **Dose Modification Guidelines** below). Pretreatment with or concomitant use of antiemetics should be considered.

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 events 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.

General

Do not administer as a bolus injection or an undiluted solution. Rapid infusion may increase the risk of infusion-related reactions (see **WARNINGS—Infusion Reactions**).

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.

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

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, Pharmacokinetics**).

Patients should be carefully monitored for toxicity. Adverse events, 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 event, 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 12: 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 toxicity.** 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	**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 diameter.) 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 13: Hematological Toxicity

GRADE	ANC	PLATELETS	MODIFICATION
1	1500 – 1900	75,000 - 150,000	Resume treatment with no dose reduction
2	1000 - <1500	50,000 - <75,000	Wait until ANC ≥1,500 and platelets ≥ 75,000; redose with no dose reduction
3	500 – 999	25,000 - <50,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction
4	<500	<25,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose at 25% dose reduction or continue full dose with cytokine support.

Table 14: 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 experience 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.

Patients with Impaired Hepatic Function

Limited clinical experience exists in treating hepatically impaired patients with DOXIL®. Based on experience with doxorubicin HCl, it is recommended that DOXIL® dosage be reduced if the bilirubin is elevated as follows: serum bilirubin 1.2 to 3.0 mg/dL give 1/2 normal dose, > 3 mg/dL give 1/4 normal dose.

Preparation for Intravenous Administration

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.

Storage and Stability

Refrigerate unopened vials of DOXIL® at 2°C to 8°C (36°F to 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®.

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.[2-8]

HOW SUPPLIED

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 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 15

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

REFERENCES

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice Pittsburgh, PA: Oncology Nursing Society; 1999:32-41.
2. Recommendations for the safe handling of parenteral antineoplastic drugs. Washington, DC: Division of Safety, National Institutes of Health; 1983. US Dept of Health and Human Services, Public Health Service publication NIH 83-2621.
3. AMA Council on Scientific Affairs. Guidelines for handling parenteral antineoplastics. JAMA. 1985; 253:1590-1592.
4. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. 1987. Available from Louis P. Jeffrey, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
5. Clinical Oncologic Society of Australia: Guidelines and recommendations for safe handling of antineoplastic agents. Med. J. Australia 1983; 1:426-428.
6. Jones RB, Frank R, Mass T. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. Ca-A Cancer Journal for Clin. 1983; 33:258-263.
7. American Society of Hospital Pharmacists. ASHP technical assistance bulletin on handling cytotoxic and hazardous drugs. AM J Hosp Pharm. 1990; 47:1033-1049.
8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines.). Am J Health-Syst Pharm. 1996;53-1669-1685.

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