

Doxil[®] Package Insert

DRAFT

Doxil[®]

[*däk'sil*]

(doxorubicin HCl liposome injection)

FOR INTRAVENOUS INFUSION ONLY

A product of ALZA Pharmaceuticals

A division of ALZA Corporation

Palo Alto, CA 94303 USA

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Date revised: [06/29/9906/28/99](#); [9:23 AM2:58 PM](#)

WARNINGS

1. Experience with Doxil® (doxorubicin HCl liposome injection) at high cumulative doses is too limited to have established its effects on the myocardium. It should therefore be assumed that Doxil® will have myocardial toxicity similar to conventional formulations of doxorubicin HCl. Irreversible myocardial toxicity leading to congestive heart failure often unresponsive to cardiac supportive therapy may be encountered as the total dosage of doxorubicin HCl approaches 550 mg/m². Prior use of other anthracyclines or anthracenediones will reduce the total dose of doxorubicin HCl that can be given without cardiac toxicity. Cardiac toxicity also may occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy.

Doxil® should be administered to patients with a history of cardiovascular disease only when the benefit outweighs the risk to the patient.

2. Acute infusion-associated reactions (flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension) have occurred in about 5% 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. 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.

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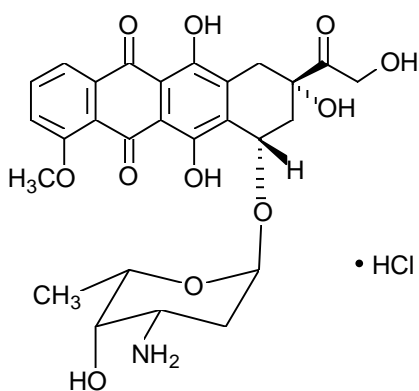
DESCRIPTION

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 C₂₇ H₂₉ NO₁₁·HCl; its molecular weight is 579.99.

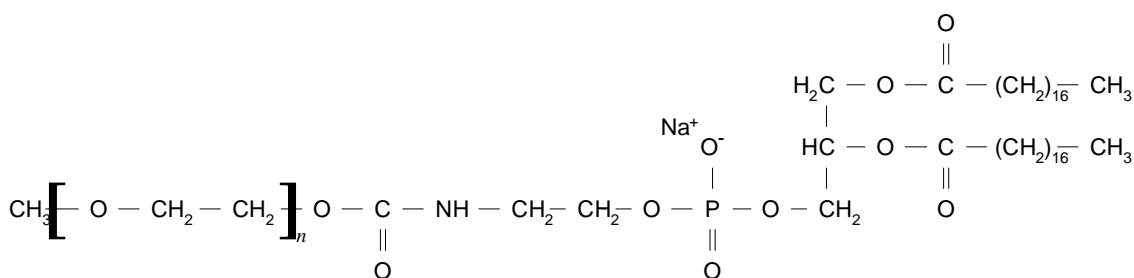
Doxil[®] is provided as a sterile, translucent, red liposomal dispersion in 10-mL glass, single use vials. Each vial contains 20 mg doxorubicin HCl at a

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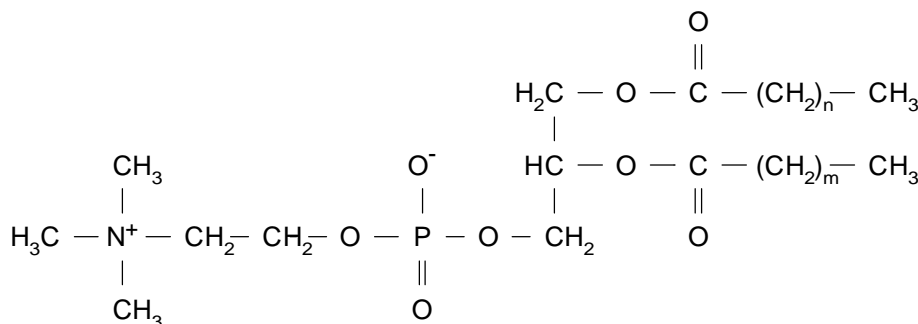
concentration of 2 mg/mL and a pH of 6.5. The STEALTH® liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 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

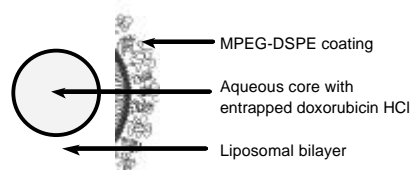
CLINICAL PHARMACOLOGY

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[®]

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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/m² administered by a 30-minute infusion. Twenty-three of these patients received single doses of both 10 and 20 mg/m² with a 3-week wash-out period between doses. The pharmacokinetic parameter values of Doxil[®], given for total doxorubicin (mostly liposomally bound), are shown in the following table.

Pharmacokinetic Parameters of Doxil[®] in AIDS Patients with Kaposi's Sarcoma

Parameter (units)	Dose	
	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 ₂) 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/m². 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/m² 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/m² dose. The exposure (AUC) is thus

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expected to be more than proportional at a 50 mg/m² 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/m², 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 mg/mL) in the plasma of patients who received 10 or 20 mg/m² Doxil[®].

Excretion: The plasma clearance of Doxil[®] was slow, with a mean clearance value of 0.041 L/h/m² at a dose of 20 mg/m². This is in contrast to doxorubicin, which displays a plasma clearance value ranging from 24 to 35 L/h/m².

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/m² 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 Carcinoma

Doxil® (doxorubicin HCl liposome injection) was studied in three open-label, single-arm, clinical trials of 176 patients with metastatic ovarian carcinoma. One hundred forty-six (146) of these patients were refractory to both paclitaxel- and platinum-based chemotherapy regimen. Refractory patients are defined as those having progressive disease while on treatment, or within 6 months of completing treatment. Patients in these studies received Doxil® at 50 mg/m² 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 refractory patients are shown in the following table .

**Patient Demographics for Refractory Patients
from Phase 2 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 phase 2 trials are given in the following table:

Response Rates in Refractory Patients from single arm Ovarian Cancer Studies

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	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 trials 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.

Preliminary Results of Ovarian Cancer Randomized Trial

Data were also provided from an interim analysis of a randomized comparative study of Doxil®. Of the 44 patients in the Doxil® arm with tumors refractory to paclitaxel and platinum compounds, 6 had objective responses, a response rate of 13.6% (95% CI 5.2% to 27.4%).

AIDS-Related Kaposi's Sarcoma

Doxil® was studied in an open-label, single-arm, multicenter study utilizing Doxil® at 20 mg/m² 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/mm³. Their age ranged from 24 to 54 years, with a mean age of 38 years. Using the ACTG staging criteria,¹ 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.

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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/m² and ranged from 20 to 620 mg/m².

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.¹ Partial response was defined as no new lesions, sites of disease, or worsening edema; flattening of $\geq 50\%$ of previously raised lesions or area of indicator lesions decreasing by $\geq 50\%$; 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 $\geq 50\%$ 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 the tables below.

Response in Refractory^a AIDS-KS

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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

Doxil® (doxorubicin HCl liposome injection) is indicated for:

1. The treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory disease is defined as disease that has progressed while on treatment, or within 6 months of completing treatment.
2. 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.

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These indications are 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®.

WARNINGS

Cardiac Toxicity

Experience with large cumulative doses of Doxil® (doxorubicin HCl liposome injection) is limited, so that Doxil's cardiac risk, and its risk compared to conventional doxorubicin formulations, has not been adequately evaluated. At present, therefore, warnings related to the use of conventional formulation doxorubicin HCl should be observed.

Special attention must be given to the cardiac toxicity exhibited by doxorubicin HCl. Acute left ventricular failure can occur with doxorubicin, particularly in patients who have received total doxorubicin dosage exceeding the currently recommended limit of 550 mg/m². Lower (400 mg/m²) 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 and/or cardiomyopathy may be encountered after discontinuation of 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 gated radionuclide scans, have been used to monitor cardiac function during anthracycline therapy. Any of these methods should be employed to monitor potential cardiac toxicity during Doxil[®] therapy. 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 the AIDS-KS studies, 68 (9.6%) patients experienced cardiac-related adverse events. In 30 patients (4.3%), the event was thought to be possibly or probably related to Doxil[®]. Nine cases of possibly or probably related cardiomyopathy and/or congestive heart failure were reported. Seven (1.0%) of the possibly or probably related cardiac events were severe. These severe events included arrhythmia (nonspecific), cardiomyopathy, heart failure, pericardial effusion, and tachycardia. Three patients discontinued study due to cardiac events.

Myelosuppression

In ovarian cancer patients, myelosuppression was generally moderate and reversible. Anemia was the most common hematologic adverse event (52.6%), followed by neutropenia (51.7%), leukopenia (42.2%) and thrombocytopenia (24.2%).

In ovarian cancer patients, 3.3% received G-CSF (or GM-CSF) to support their blood counts. (See **DOSAGE AND ADMINISTRATION, Dose Modification Guidelines.**)

In AIDS-KS patients, 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, even at the recommended dose of 20 mg/m². Leukopenia is the most common adverse event (about 60%) experienced in this population; anemia (about 20%) and thrombocytopenia

(about 10%) 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, and 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, characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest and throat, and/or hypotension have occurred in 5% 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 resolves when the rate of infusion is slowed. The majority of infusion-related events occurred during the first infusion. Six AIDS-KS patients (0.9%) and 13 (1.7%) solid tumor patients discontinued Doxil® therapy because of infusion-related reactions. 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.**)

Palmar-Plantar Erythrodysesthesia

In ovarian cancer patients, 37.4% of patients experienced PPE (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 16.4% of the patients reporting Grade 3 or 4 events. Thirteen (3.5%) of the ovarian cancer patients discontinued treatment due to PPE or other skin toxicity. (See definitions of PPE grades in **DOSAGE AND ADMINISTRATION, Dose Modification Guidelines.**)

Among 705 patients with AIDS-related Kaposi's sarcoma treated with Doxil® at 20 mg/m², 24 (3.4%) developed PPE, with 3 (0.9%) discontinuing.

PPE was generally seen 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 PPE. (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/m² human dose on a mg/m² 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[®] have not been adequately evaluated in patients with hepatic impairment. 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.

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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/m² human dose on a mg/m² basis). Decreased testicular weights and hypospermia were present in rats after repeat doses \geq 0.25 mg/kg/day (about one thirtieth the 50 mg/m² human dose on a mg/m² 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/m² human dose on a mg/m² 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 the conventional formulation of

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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, 29% were 60 to 69 years old, while 22.8% were 70 years and over. No overall differences were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. There are insufficient data for a comparative evaluation of efficacy according to age.

Radiation Therapy

Recall of skin reaction due to prior radiotherapy has occurred with Doxil[®] administration.

Information for the Patient (See Patient Package Insert)

Patients and patients' caregivers should be informed of the expected adverse effects of Doxil[®], particularly hand-foot syndrome, stomatitis, and neutropenia and its complications of neutropenic fever, infection, and sepsis.

Hand-Foot Syndrome (Palmar-Plantar Erythrodysesthesia): 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 of 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.

ADVERSE REACTIONS

Ovarian Cancer Patients

Safety data are available from 373 ovarian cancer patients treated with Doxil[®] in 4 clinical studies. The patient population was predominantly white (93.6%) with a median age of 60 years. Patients received a median cycle dose of 50 mg/m² administered with a median cycle length of 29.5 days. They remained on study drug for a median of 56 days and received a median cumulative dose of 137.5 mg/m². Patients received a median of 3- cycles of Doxil[®], although some patients remained on study drug for a prolonged period, with 46 patients (12.3%) receiving more than 10 cycles of treatment.

Adverse events (AEs) were reported in all but 2 of the 361 patients who had at least one AE form collected. A total of 3,124 AEs were reported, an average of 8.6 AEs per patient. Most (91.7%) patients had AEs that were considered related to study drug.

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**Drug-Related Adverse Events
 Reported in ≥ 5% of Ovarian Cancer Patients**

Adverse Effect	% Ovarian Patients
Hematologic (n=373)	
Leukopenia	
< 4,000/mm ³	42.2
< 1,000/mm ³	8.3
G-CSF or GM-CSF support*	3.3
Neutropenia	
<2000/mm ³	51.7
<500/mm ³	8.3
Febrile neutropenia	0.3
Anemia	
<10 g/dL	52.6
<8 g/dL	25.0
RBC transfusions	12.9
Epoetin alpha support*	2.1
Thrombocytopenia	
<150,000/mm ³	24.2
<25,000/mm ³	1.1
Platelet transfusions*	1.4
Non-Hematologic (n=361)	
Palmar-plantar erythrodysesthesia	
All Grades	37.4
Grade 3 & 4	16.4
Stomatitis	
All Grades	37.4
Grade 3 & 4	7.7
Nausea	
All Grades	37.7
Grade 3 & 4	4.2
Asthenia	33.0
Vomiting	22.4
Rash	21.6
Alopecia	15.2
Constipation	12.7
Anorexia	11.9
Mucous Membrane Disorder	11.6
Diarrhea	10.0
Abdominal Pain	8.0
Paresthesia	7.8
Pain	7.2
Fever	6.9
Pharyngitis	5.5
Dry Skin	5.5
Headache	5.3

*From concomitant medication or transfusion logs, not reported as AEs.

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The following additional (not in table) adverse events were observed in ovarian cancer patients with doses administered every four weeks; only events considered at least possibly drug-related by investigators are included.

Incidence 1% to 5%

Body as a Whole: allergic reaction, chills, infection, chest pain, back pain, abdomen enlarged, malaise.

Digestive System: dyspepsia, oral moniliasis, mouth ulceration, esophagitis, dysphagia.

Metabolic and Nutritional System: peripheral edema, dehydration.

Musculoskeletal System: myalgia.

Nervous System: somnolence, dizziness, depression, insomnia, anxiety.

Respiratory System: dyspnea, cough increased, rhinitis.

Cutaneous: pruritus, skin discoloration, skin disorder, vesiculobullous rash, maculopapular rash, exfoliative dermatitis, herpes zoster, sweating.

Special Senses: conjunctivitis, taste perversion.

Incidence Less Than 1%

Body As A Whole: cellulitis, anaphylactoid reaction, ascites, flu syndrome, neck pain, moniliasis, injection site pain, face edema, chills and fever, pelvic pain, chest pain substernal, injection site inflammation.

Cardiovascular System: hypertension, angina pectoris, pericardial effusion, postural hypotension, hypotension, palpitation, syncope, shock, bradycardia, arrhythmia, phlebitis, tachycardia, cardiomegaly, heart failure, hemorrhage.

Digestive System: gingivitis, eructation, increased salivation, melena, gastrointestinal hemorrhage, proctitis, jaundice, ileus, periodontal abscess, flatulence, aphthous stomatitis, gastritis, glossitis, gum hemorrhage.

Hemic and Lymphatic System: hypochromic anemia, lymphadenopathy, ecchymosis, petechia.

Metabolic/Nutritional Disorders: SGOT increase, creatinine increase, hypocalcemia, hyperglycemia, hypokalemia, hypermagnesemia, hyponatremia, weight gain, bilirubinemia, generalized edema, cachexia, hypochloremia.

Musculoskeletal System: arthralgia, bone pain, myasthenia.

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Nervous System: peripheral neuritis, incoordination, thinking abnormal, confusion, hypertonia, nervousness, hyperesthesia, hypesthesia, neuropathy, ataxia.

Respiratory System: pleural effusion, asthma, hiccup, pneumothorax, laryngitis, sinusitis, voice alteration, epistaxis, pneumonia.

Skin and Appendages: skin ulcer, herpes simplex, contact dermatitis, fungal dermatitis, furunculosis, skin nodule, urticaria, acne.

Special Senses: amblyopia, blepharitis, parosmia, taste loss.

Urogenital System: urinary tract infection, leukorrhea, cystitis, nocturia, dysuria, breast pain, mastitis, oliguria, vaginitis, kidney function abnormal, vaginal hemorrhage, hydronephrosis, vaginal moniliasis.

AIDS-KS Patients

Information on adverse events is based on the experience reported in 753 patients with AIDS-related KS enrolled in four studies. The majority of patients were treated with 20 mg/m² of Doxil[®] (doxorubicin HCl liposome injection) 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/m² and ranged from 3.3 to 798.6 mg/m². Twenty-six patients (3.0%) received cumulative doses of greater than 450 mg/m².

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/mm³, with 50.8% of patients having less than 50 cells/mm³. The mean absolute neutrophil count at study entry was approximately 3000 cells/mm³.

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%

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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, palmar-plantar erythrodysesthesia, pneumonia, cough/dyspnea, fatigue, optic neuritis, progression of a non-KS tumor, allergy to penicillin, and unspecified reasons.

**Probably and Possibly Drug-Related Adverse Events
Reported in ≥ 5% of AIDS-KS Patients**

	Refractory or Intolerant AIDS-KS Patients	Total AIDS-KS Patients
Number of Patients	77	705
Number of Patients Reporting Adverse Events	57 (74.0%)	586 (83.1%)
Adverse Event		
Neutropenia (ANC <1000/mm ³)	34 (44.2%)	352 (49.9%)
Anemia	5 (6.5%)	137 (19.4%)
Nausea	14 (18.2%)	119 (16.9%)
Asthenia	5 (6.5%)	70 (9.9%)
Hypochromic Anemia	4 (5.2%)	69 (9.8%)
Thrombocytopenia	5 (6.5%)	65 (9.2%)
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 events were observed in AIDS-KS patients; 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 System: mouth ulceration, glossitis, constipation, aphthous stomatitis, anorexia, dysphagia, abdominal pain.

Hematologic: hemolysis, increased prothrombin time.

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

Digestive System: dyspepsia, cholestatic jaundice, gingivitis, gastritis, 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 System: diabetes mellitus.

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

Metabolic/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.

Musculoskeletal System: myalgia, arthralgia, bone pain, myositis.

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

Respiratory System: 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 System: hematuria, balanitis, cystitis, dysuria, genital edema,

glycosuria, kidney failure.

OVERDOSAGE

Acute overdosage with doxorubicin HCl causes increases in mucositis, leukopenia 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

Ovarian Cancer Patients

Doxil[®] (doxorubicin HCl liposome injection) should be administered intravenously at a dose of 50 mg/m² (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 PPE, 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.

AIDS-KS Patients

Doxil[®] (doxorubicin HCl liposome injection) should be administered intravenously at a dose of 20 mg/m² (doxorubicin HCl equivalent) over 30 minutes, 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**.)

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Each vial contains 20 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/m²; 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 PPE, 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

PALMAR - PLANTAR ERYTHRODYSESTHESIA	
Toxicity Grade	Dose Adjustment

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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 diam.)	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.
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.

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

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4	<500	<25,000	Wait until ANC \geq 1,500 and platelets \geq 75,000; redose at 25% dose reduction or continue full dose with cytokine support.
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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.
3 (painful erythema, edema, or ulcers, but 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 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 ½ normal dose, >3 mg/dL give ¼ normal dose.

Preparation for Intravenous Administration

The appropriate dose of Doxil®, up to a maximum of 90 mg, must be diluted in 250 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.

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

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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 glass, single use vials.

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

Refrigerate at 2-8°C. 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[®].

Available as individually cartoned vials in packages of six. NDC #61471-295-12.

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