

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**50-718/S-019**

***Trade Name:*** Doxil

***Generic Name:*** doxorubicin HCL liposome injection

***Sponsor:*** Johnson & Johnson Pharmaceutical  
Research & Development, LLC

***Approval Date:*** October 27, 2004

***Purpose:*** Provides for significant changes to the following sections of the product labeling - BOX WARNING, WARNINGS, PRECAUTIONS (Information for the Patient), DOSAGE AND ADMINISTRATION (AIDS-KS Patients, Dose Modifications and Preparation for Intravenous Administration)

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*APPLICATION NUMBER:*

**50-718/S-019**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**50-718/S-019**

**APPROVAL LETTER**



NDA 50-718/S-019

Johnson & Johnson Pharmaceutical Research & Development, LLC  
c/o Alza Corporation  
Attention: Brian Maloney, R.Ph., M.Sc.  
Associate Director, Regulatory Affairs  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your supplemental new drug application dated October 16, 2003, received December 29, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doxil® (doxorubicin HCl liposome injection).

We acknowledge receipt of your submission dated October 28, 2003 received October 29, 2003. We also acknowledge receipt of your submission dated March 28, 2002 containing the FPL for supplement 010. We note that this FPL was superseded by the FPL for supplement 010 dated August 5, 2003 and acknowledged and retained on March 18, 2004.

This supplemental new drug application provides significant changes to the following sections of the product labeling – **BOX WARNING, WARNINGS, PRECAUTIONS (Information for the Patient), DOSAGE AND ADMINISTRATION (AIDS-KS Patients, Dose Modifications and Preparation for Intravenous Administration)**. The reference to “Doxil” has been changed “DOXIL” throughout the package insert. Also minor editorial changes were made to provide additional guidance to prescribing physicians.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 50-718/S-019". Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.  
Director  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Richard Pazdur  
10/27/04 03:37:48 PM

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**50-718/S-019**

**LABELING**

**DOXIL®**  
**(doxorubicin HCl) liposome injection**

**Revised Draft Labeling**

**BOX WARNING**

**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<sup>2</sup>. 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<sup>2</sup> every 4 weeks. At all cumulative anthracycline doses between 450 – 500 mg/m<sup>2</sup> or between 500 – 550 mg/m<sup>2</sup>, 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<sup>®</sup> for doxorubicin HCl has resulted in severe side effects. DOXIL<sup>®</sup> should not be substituted for doxorubicin HCl on a mg per mg basis. **(See DESCRIPTION and DOSAGE AND ADMINISTRATION.)**
6. DOXIL<sup>®</sup> should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

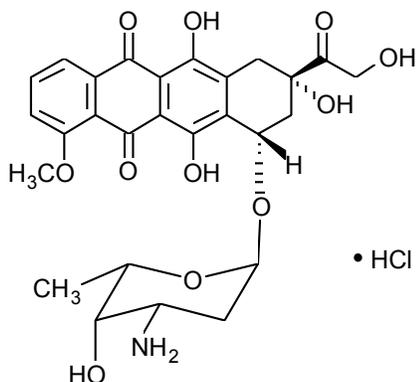
## DESCRIPTION

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

**Note: Liposomal encapsulation can substantially affect a drug's functional properties relative to those of an unencapsulated formulation. 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 (8S,10S)-10-[(3-amino-2,3,6-trideoxy- $\alpha$ -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  $C_{27}H_{29}NO_{11} \cdot HCl$ ; its molecular weight is 579.99.

DOXIL<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> liposomes.

MPEG-DSPE has the following structural formula:  
(Chemical structure shown here)

### ***Clinical Pharmacology***

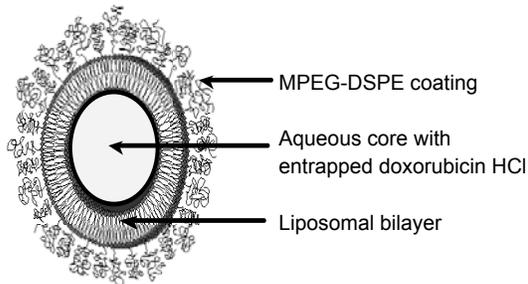
#### **Mechanism of Action**

The active ingredient of DOXIL<sup>®</sup> 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<sup>®</sup> is doxorubicin HCl encapsulated in long-circulating STEALTH<sup>®</sup> liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH<sup>®</sup> liposomes of DOXIL<sup>®</sup> 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<sup>®</sup> liposome:



STEALTH<sup>®</sup> 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<sup>®</sup> liposomes are able to penetrate the altered and often compromised vasculature of tumors. This hypothesis is supported by studies using colloidal gold-containing STEALTH<sup>®</sup> liposomes, which can be visualized microscopically. Evidence of penetration of STEALTH<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> were evaluated in 42 patients with AIDS-related Kaposi's sarcoma (KS) who received single doses of 10 or 20 mg/m<sup>2</sup> administered by a 30-minute infusion. Twenty-three of these patients received single doses of both 10 and 20 mg/m<sup>2</sup> with a 3-week wash-out period between doses. The pharmacokinetic parameter values of DOXIL<sup>®</sup>, given for total doxorubicin (mostly liposomally bound), are presented in the following table.

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### Pharmacokinetic Parameters of DOXIL<sup>®</sup> in Patients with AIDS-related Kaposi's Sarcoma

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Parameter (units)	Dose	
	10 mg/m <sup>2</sup>	20 mg/m <sup>2</sup>
Peak Plasma Concentration (µg/mL)	4.12 ± 0.215	8.34 ± 0.49
Plasma Clearance (L/h/m <sup>2</sup> )	0.056 ± 0.01	0.041 ± 0.004
Steady State Volume of Distribution (L/m <sup>2</sup> )	2.83 ± 0.145	2.72 ± 0.120
AUC (µg/mL•h)	277 ± 32.9	590 ± 58.7
First Phase (λ <sub>1</sub> ) Half-Life (h)	4.7 ± 1.1	5.2 ± 1.4
Plasma Clearance (L/h/m <sup>2</sup> )	0.056 ± 0.01	0.041 ± 0.004

N = 23

Mean ± Standard Error

DOXIL<sup>®</sup> displayed linear pharmacokinetics over the range of 10 to 20 mg/m<sup>2</sup>. Disposition occurred in two phases after DOXIL<sup>®</sup> 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<sup>®</sup> at a 50 mg/m<sup>2</sup> dose is reported to be nonlinear. At this dose, the elimination half-life of DOXIL<sup>®</sup> is expected to be longer and the clearance lower compared to a 20 mg/m<sup>2</sup> dose. The exposure (AUC) is thus expected to be more than proportional at a 50 mg/m<sup>2</sup> 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<sup>2</sup>, the small steady state volume of distribution of DOXIL<sup>®</sup> shows that DOXIL<sup>®</sup> is confined mostly to the vascular fluid volume. Plasma protein binding of DOXIL<sup>®</sup> 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<sup>2</sup> DOXIL<sup>®</sup>.

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

Because of its slower clearance, the AUC of DOXIL<sup>®</sup>, 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<sup>®</sup> 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<sup>®</sup> 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<sup>2</sup> DOXIL<sup>®</sup> in 11 patients. The concentration of DOXIL<sup>®</sup> 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<sup>®</sup> are delivered to KS lesions than to normal skin.

### ***Clinical Studies***

#### **Ovarian Carcinoma**

DOXIL<sup>®</sup> (doxorubicin HCl) liposome injection was studied in three open-label, single-arm, clinical trials of 176 patients with metastatic ovarian carcinoma. 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<sup>®</sup> at 50 mg/m<sup>2</sup> 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 the following table.

### Patient Demographics for Patients with Refractory Ovarian Cancer 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 <sup>2</sup> )			
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 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 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/m<sup>2</sup> 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<sup>3</sup>. Their age ranged from 24 to 54 years, with a mean age of 38 years. Using the ACTG staging criteria, 178% 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<sup>2</sup> and ranged from 20 to 620 mg/m<sup>2</sup>.

Two analyses of tumor response were used to evaluate the effectiveness of DOXIL<sup>®</sup>: 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.<sup>1</sup> 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.

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### **Response in Patients with Refractory<sup>a</sup> AIDS-KS**

Investigator Assessment	All Evaluable Patients (n = 34)	Evaluable Patients Who Received Prior Doxorubicin (n = 20)
Response <sup>b</sup>		
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 <sup>b</sup>		
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

<sup>a</sup> Patients with disease that progressed on prior combination chemotherapy or who were intolerant to such therapy.

<sup>b</sup> There were no complete responses in this population.

## INDICATIONS AND USAGE

DOXIL<sup>®</sup> (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.

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<sup>®</sup> (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<sup>®</sup>.

DOXIL<sup>®</sup> 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<sup>2</sup>. Lower (400 mg/m<sup>2</sup>) 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<sup>®</sup> only when the potential benefit of treatment outweighs the risk.

Cardiac function should be carefully monitored in patients treated with DOXIL<sup>®</sup>. 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<sup>®</sup>. If these test results indicate possible cardiac injury associated with DOXIL<sup>®</sup> 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<sup>®</sup> at starting dose of 50 mg/m<sup>2</sup> every 4 weeks. At all cumulative anthracycline doses between 450 – 500 mg/m<sup>2</sup> or between 500 – 550 mg/m<sup>2</sup>, the risk of cardiac toxicity for patients treated with DOXIL<sup>®</sup> 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)**

**Number of Patients**

	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 & symptoms of CHF only	2

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.

## **Myelosuppression**

In patients with relapsed ovarian cancer, myelosuppression was generally moderate and reversible. Anemia was the most common hematologic adverse event (52.6%), followed by leukopenia (WBC < 4000 mm<sup>3</sup>; 42.2%), thrombocytopenia (24.2%), and neutropenia [ANC <1000] (19.0%) **(See Hematology Data table in ADVERSE REACTIONS, Ovarian Cancer Patients.)**

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

For patients with AIDS-KS, 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<sup>2</sup> **(see Hematology Data table in ADVERSE REACTIONS, AIDS-KS 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<sup>®</sup>. 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<sup>®</sup>, 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<sup>®</sup> 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<sup>®</sup> may potentiate the toxicity of other anticancer therapies. In particular, hematologic toxicity may be more severe when DOXIL<sup>®</sup> 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, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and/or hypotension have occurred in up to 10% of patients treated with DOXIL<sup>®</sup>. 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. Six patients with AIDS-KS (0.9%) and 13 (1.7%) patients with solid tumor discontinued DOXIL<sup>®</sup> 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<sup>®</sup> 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 patients with ovarian cancer patients, 37.4% of 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 16.4% of the patients reporting Grade 3 or 4 events. Thirteen (3.5%) of the patients with ovarian cancer 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<sup>®</sup> at 20 mg/m<sup>2</sup>, 24 (3.4%) developed HFS, with 3 (0.9%) discontinuing.

HFS 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 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<sup>®</sup> can cause fetal harm when administered to a pregnant woman. DOXIL<sup>®</sup> 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<sup>2</sup> human dose on a mg/m<sup>2</sup> 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<sup>®</sup> 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<sup>®</sup>, 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<sup>®</sup> 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<sup>®</sup> is not a vesicant, but should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of DOXIL<sup>®</sup>, 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<sup>®</sup> must not be given by the intramuscular or subcutaneous route.

In studies with rabbits, lesions that were induced by subcutaneous injection of DOXIL<sup>®</sup> 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<sup>®</sup> have not been adequately evaluated in patients with hepatic impairment. Doxorubicin is eliminated in large part by the liver. Thus, DOXIL<sup>®</sup> dosage should be reduced in patients with impaired hepatic function. **(See DOSAGE AND ADMINISTRATION.)**

Prior to DOXIL<sup>®</sup> 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<sup>®</sup>, doxorubicin HCl and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models.

STEALTH<sup>®</sup> 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<sup>®</sup> 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<sup>2</sup> human dose on a mg/m<sup>2</sup> 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/m<sup>2</sup> human dose on a mg/m<sup>2</sup> 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<sup>2</sup> human dose on a mg/m<sup>2</sup> basis).

## **PRECAUTIONS**

### **General**

Patients receiving therapy with DOXIL<sup>®</sup> 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<sup>®</sup>.

### **Drug Interactions**

No formal drug interaction studies have been conducted with DOXIL<sup>®</sup>. Until specific compatibility data are available, it is not recommended that DOXIL<sup>®</sup> be mixed with other drugs. DOXIL<sup>®</sup> 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<sup>®</sup>, mothers should discontinue nursing prior to taking this drug.

### **Pediatric Use**

The safety and effectiveness of DOXIL<sup>®</sup> in pediatric patients have not been established.

### **Geriatric Use**

Of the 373 patients with ovarian cancer, 29% were 60 to 69 years old, while 22.8% were 70 years and over. No overall differences were observed between these patients and younger patients, 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<sup>®</sup> 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 its 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 373 patients with ovarian cancer 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/m<sup>2</sup> 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/m<sup>2</sup>. 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.

**Hematology Data Reported in Patients with Ovarian Cancer**

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	% Ovarian Patients (n=373)
Neutropenia	
<1000/mm <sup>3</sup>	19.0
<500/mm <sup>3</sup>	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 <sup>3</sup>	24.2
<25,000/mm <sup>3</sup>	1.1
Platelet transfusions*	1.4

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

Non-Hematologic Adverse Event	% Ovarian Patients (n=361)
Hand Foot Syndrome (HFS)	
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

**The following additional (not in table) adverse events 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 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.

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.

### **Patients with AIDS-KS**

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/m<sup>2</sup> of DOXIL<sup>®</sup> (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/m<sup>2</sup> and ranged from 3.3 to 798.6 mg/m<sup>2</sup>. Twenty-six patients (3.0%) received cumulative doses of greater than 450 mg/m<sup>2</sup>.

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<sup>3</sup>, with 50.8% of patients having less than 50 cells/mm<sup>3</sup>. The mean absolute neutrophil count at study entry was approximately 3000 cells/mm<sup>3</sup>.

Patients received a variety of potentially myelotoxic drugs in combination with DOXIL<sup>®</sup>. 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<sup>®</sup> clinical trials, adverse event information was available for 705 patients. In many instances it was difficult to determine whether adverse events resulted from DOXIL<sup>®</sup>, 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<sup>®</sup>.

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.

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#### Hematology Data Reported in Patients with AIDS-KS

	Patients with Refractory or Intolerant AIDS-KS (n = 74)		Total Patients with AIDS-KS (n = 720)	
Neutropenia				
< 1000/mm <sup>3</sup>	34	(45.9%)	352	(48.9%)
< 500/mm <sup>3</sup>	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 <sup>3</sup>	45	(60.8%)	439	(60.9%)
< 25,000/mm <sup>3</sup>	1	(1.4%)	30	(4.2%)

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#### Probably and Possibly Drug-Related Non-Hematologic Adverse Events Reported in ≥ 5% of Patients with AIDS-KS

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Adverse Event	Patients with Refractory or Intolerant AIDS-KS (n = 77)		Total Patients with AIDS-KS (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-KS; 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, 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 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*****Patients with Ovarian Cancer**

DOXIL<sup>®</sup> (doxorubicin HCl) liposome injection should be administered intravenously at a dose of 50 mg/m<sup>2</sup> (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.

**AIDS-KS Patients**

DOXIL<sup>®</sup> (doxorubicin HCl) liposome injection should be administered intravenously at a dose of 20 mg/m<sup>2</sup> (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<sup>®</sup> be mixed with other drugs.

DOXIL<sup>®</sup> should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of DOXIL<sup>®</sup>, 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<sup>®</sup> must not be given by the intramuscular or subcutaneous route.

**Dose Modification Guidelines**

DOXIL<sup>®</sup> exhibits nonlinear pharmacokinetics at 50 mg/m<sup>2</sup>; 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**

**(Hand Foot Syndrome) (HFS)**

Toxicity Grade

Dose Adjustment

1 (mild erythema, swelling, or desquamation not interfering with daily activities)

**Redose unless patient has experienced previous Grade 3 or 4 HFS.** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.

2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter.)

**Delay dosing for up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, DOXIL<sup>®</sup> should be discontinued. If resolved to Grade 0-1 within 2 weeks, and there was no prior Grade 3-4 HFS, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.

3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)

**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, DOXIL<sup>®</sup> 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<sup>®</sup> should be discontinued.

<b>HEMATOLOGICAL TOXICITY</b>
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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 $\geq$ 1,500 and platelets $\geq$ 75,000; redose with no dose reduction
3	500 – 999	25,000 - <50,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose with no dose reduction
4	<500	<25,000	Wait until ANC $\geq$ 1,500 and platelets $\geq$ 75,000; redose at 25% dose reduction or continue full dose with cytokine support.

### STOMATITIS

Toxicity Grade	Dose Adjustment
1 (painless ulcers, erythema, or mild soreness)	<b>Redose unless patient has experienced previous Grade 3 or 4 stomatitis.</b> 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)	<b>Delay dosing for up to 2 weeks or until resolved to Grade 0-1.</b> If after 2 weeks there is no resolution, DOXIL <sup>®</sup> should be discontinued. If resolved to Grade 0-1 within 2 weeks, and there was no prior Grade 3-4 stomatitis, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.
3 (painful erythema, edema, or ulcers, and cannot eat)	<b>Delay dosing up to 2 weeks or until resolved to Grade 0-1.</b> Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, DOXIL <sup>®</sup> should be discontinued.
4 (requires parenteral or enteral support)	<b>Delay dosing up to 2 weeks or until resolved to Grade 0-1.</b> Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, DOXIL <sup>®</sup> should be discontinued.

### Patients with Impaired Hepatic Function

Limited clinical experience exists in treating hepatically impaired patients with DOXIL<sup>®</sup>. Based on experience with doxorubicin HCl, it is recommended that DOXIL<sup>®</sup> 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**

DOXIL<sup>®</sup> 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<sup>®</sup>. Diluted DOXIL<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>.

### Procedure for Proper Handling and Disposal

Caution should be exercised in the handling and preparation of DOXIL<sup>®</sup>.

The use of gloves is required.

If DOXIL<sup>®</sup> comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

DOXIL<sup>®</sup> should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of DOXIL<sup>®</sup>, 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<sup>®</sup> must not be given by the intramuscular or subcutaneous route.

DOXIL<sup>®</sup> should be handled and disposed of in a manner consistent with other anticancer drugs. Several guidelines on this subject exist.<sup>2-8</sup>

### **How Supplied**

DOXIL<sup>®</sup> (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. 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<sup>®</sup>.

The following packages of six individually cartoned vials are available:

mg in vial	fill volume	vial size	NDC #s
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## 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, MA 02115.
5. Clinical Oncological 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 J 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-SystPharm. 1996;53:1669-1685.

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*APPLICATION NUMBER:*

**50-718/S-019**

**MEDICAL REVIEW(S)**

# Clinical Review Cover Sheet

Application	NDA 50-718 SE8-019
Drug Name	Doxorubicin HCl liposome injection
Trade Name	Doxil
Medical Reviewer	Qin Ryan, MD, PhD
Medical Team Leader	Ramzi Dagher, MD
Documents reviewed	N50-718 SE8-019 (10/16/03 and 10/28/03) IND 36778 N-357 IM (9/25/03)

# CLINICAL REVIEW

## Executive Summary Section

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# Clinical Review for sNDA 50-718

## Executive Summary

### I. Recommendations

#### A. Recommendation on Approvability

The DODP, CDER, USFDA recommends approval of the supplemental NDA application for Doxil with the following revisions to the sponsor proposed label based on data from studies in metastatic breast cancer and cancer patients previously exposed to anthracyclines:

1. The Doxil label revision should only include data of Doxil exposure and toxicity, but should not include the comparative cardiac toxicity data for doxorubicin (see section II C of the executive summary for further details).
2. The label revisions regarding clinical management of palmar plantar erythema (PPE), mucositis and infusion reactions are acceptable.
3. The cardiac biopsy data are exploratory and should not be included in the label.

It should be noted that no new indication is proposed. Doxil is currently approved for the second line treatment of patients with ovarian carcinoma and for the second line treatment of patients with Kaposi sarcoma related to AIDS.

#### B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Not applicable

### II. Summary of Clinical Findings

#### A. Brief Overview of Clinical Program

Doxil is a liposomal doxorubicin IV formulation and had received accelerated approval for systemic chemotherapy refractory AIDS-related KS and ovarian carcinoma. This supplemental NDA has proposed an amendment for the Doxil safety profile. Specifically, a cardiac toxicity comparison of Doxil and doxorubicin, cardiac biopsy data in patients who had prior Doxil with or without doxorubicin, and modification of dosing guidelines or rate of infusion for toxicities of palmar plantar erythema/hand foot syndrome, mucositis, and infusion reaction are being proposed as additions to the current label. No new efficacy

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claims or new indication, new dose/schedule/regimen, or new patient population is proposed with this supplement. The studies submitted to support this supplemental NDA are tabulated as follows:

**Table 1: Trials submitted for this sNDA review.**

Study Protocol No.	Title	Patient enrolled/treated
I97-328	A Randomized Phase 3 Trial of CAELYX™/ Doxil (SCH 200746) vs. Doxorubicin for the First- Line Treatment of Women with Metastatic Breast Cancer	Doxil 254/250 Doxorubicin 255/250
I96-352	A Randomized Multicenter Trial of CAELYX/DOXIL (SCH 200746) as Monotherapy vs. a Comparative Salvage Regimen for the Treatment of Subjects With Advanced Breast Cancer who have Failed a Prior Taxane Containing Regimen	Doxil 150/146 Navelbine 129/129 Mitomycin + vicristine 22/22
30-58	Assessment of Cardiotoxicity by Endomyocardial Biopsy in Patients with Advanced Malignancies Treated with DOXIL/CAELYX (doxorubicin HCl liposome injection).	8/8 (biopsy)
30-21	Assessment of Cardiotoxicity by Endomyocardial Biopsy in Patients Receiving Greater than 400 mg/m <sup>2</sup> of DOXIL.	10/10 (biopsy)

#### **B. Efficacy**

There is no new efficacy claim and no new indication is proposed.

#### **C. Safety**

A total of 404 patients with metastatic breast cancer were exposed to Doxil in studies I97-328 (N=254) and I96-352 (N=150). In trial I97-328, a total of 1444 cycles of Doxil were administered to 250 patients. The mean dose per cycle was 48.3 mg/m<sup>2</sup> for Doxil, and 58.0 mg/m<sup>2</sup> for doxorubicin. The mean cycle length was 29.6 days for Doxil, and 22.3 days for doxorubicin. The median treatment duration was 8 cycles (range: 1-15 cycles) and there were 62 (25%) patients who

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received 8 cycles at equal or more than 80% of the designated dose and 10 (4%) patients received 8 cycles at less than 80% of the designated dose. In trial I96-352, a total of 500 cycles of Doxil were administered to 146 patients. The mean cycle length with Doxil was 29.8 days and the mean cycle dose for Doxil was 48.6 mg/m<sup>2</sup>.

The sponsor has included cardiac toxicity as a progression free survival (PFS) event in the primary analysis. The sponsor reported that a total of 58 (10 Doxil, 48 doxorubicin) subjects had LVEF-defined cardiac toxicity. None of the Doxil subjects but 10 of 48 doxorubicin subjects who had left ventricular ejection fraction (LVEF)-defined cardiac toxicity also had signs and symptoms of congestive heart failure (CHF).

The sponsor claims that at cumulative doses > 450 mg/m<sup>2</sup>, the risk of cardiotoxicity for Doxil subjects did not increase; (At all cumulative anthracycline doses between 450 – 500 mg/m<sup>2</sup> or between 500-550 mg/m<sup>2</sup>, the risk of cardiac toxicity for patients treated with Doxil was 11%) whereas, with doxorubicin the risk continued to increase with further cumulative dosing. For Doxil subjects the mean % decrease in LVEF remained at approximately 2-3% regardless of cumulative dose. In contrast, for doxorubicin subjects, the mean% decrease in LVEF was positively correlated with cumulative anthracycline dose.

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Regarding cardiac toxicity, the data of Doxil exposure from study I97-328 is acceptable. The comparative cardiac toxicity of Doxil versus doxorubicin should not be included in the label. The reasons are as follows: 1) the efficacy of Doxil in the first line setting of metastatic breast cancer in comparison to doxorubicin has not been established. 2) The differences in anthracycline dose intensity and in the frequency of cardiac assessment between the two arms may have introduced bias in the cardiac toxicity finding in favor of Doxil.

The sponsor also included reports of two small studies (8 and 10 patients) of post anthracycline cardiac biopsy. The reviewer's opinion is that this data should not be included in the label due to limited sample size (8 patients) and variable prior therapy (with or without prior doxorubicin, the cumulative dose of doxorubicin and Doxil).

The frequent adverse events (AE) due to Doxil treatment observed and treatment discontinuation due to AE on studies I97-328 and I96-352 are summarized as follows:

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**Table 2: Frequent adverse events observed on Doxil treatment**

Adverse events	I97-328 (%)	I96-352 (%)
Alopecia	20	3
Fatigue	12	20
Nausea	37	31
Vomiting	19	20
Mucositis NOS	23	14
Stomatitis	22	22
PPE	48	37
Grade 3	17	18
Grade 4	0	1
Discontinued	7	8
Infusion reaction	13	12
Discontinuation due to AE	24	19

The reviewer agrees with the proposed modification of Doxil dosing or administration guidelines for hand foot syndrome (PPE/HFS), infusion reactions and mucositis/stomatitis.

#### **D. Dosing**

No new dosing regimen is proposed. The previously approved dosing regimen for 2<sup>nd</sup> line therapy in ovarian carcinoma and AIDS-KS is 50 mg/m<sup>2</sup> IV every 3-4 weeks.

#### **E. Special Populations**

Only female patients were enrolled in studies I97-328 and I96-352. In study I97-328, 60% of patients were older than age 55. 80% of patients were Caucasian and 20% were Hispanic. 16% of patients had prior anthracycline. For study I96-352, about 34% of patients were older than age 60. There were 85% Caucasian, 6.4% Asian, 7% Hispanic, and <1% others. More than 50% of patients had one prior therapy, 35% had 2 prior therapies, and 5% had more than 2 prior therapies. Seventeen percent of patients had prior anthracycline.

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### Clinical Review

#### I. Introduction and Background

##### A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established name: Doxil

Doxil is a liposomal doxorubicin IV formulation and had received accelerated approval for systemic chemotherapy refractory AIDS-related KS and ovarian carcinoma. The approved dose and schedule of Doxil for the above indication is 50 mg/m<sup>2</sup> IV every 3-4 weeks.

This submission is a supplement for a proposed label amendment regarding the Doxil safety profile in breast cancer. No efficacy claim, new indications, new dose, schedule, or regimen is proposed.

##### B. State of Armamentarium for Indication(s)

Doxil had received accelerated approval for systemic chemotherapy refractory AIDS-related KS and ovarian carcinoma. This supplemental NDA has proposed an amendment for the Doxil safety profile, specifically, cardiac toxicity comparing Doxil and doxorubicin, cardiac biopsy in cancer patients who had prior Doxil with or without doxorubicin, palmar plantar erythema/hand foot syndrome (PPE/HFS), mucositis and infusion reactions. No efficacy claims or new indication is proposed. The database is consist of 4 study reports, I97-328 (Doxil vs. doxorubicin in 1<sup>st</sup> line treatment for metastatic breast cancer), I96-352 (Doxil vs. nalvabine or mitomycin + vinblastine in 2<sup>nd</sup> or 3<sup>rd</sup> line treatment for metastatic breast cancer), 30-58 (cardiac biopsy in cancer patients previously exposed to Doxil with or without doxorubicin) and 30-21 (cardiac biopsy in cancer patients previously exposed to > 400mg/m<sup>2</sup> Doxil) (for details see Table 1: Trials submitted for this sNDA review.).

Hormones, chemotherapy drugs and biologics are approved for the treatment of metastatic breast cancer. Available chemotherapy drugs commonly used to treat metastatic breast cancer include taxanes (paclitaxel, docetaxel), cyclophosphamide, 5- FU, doxorubicin, methotrexate, thiotepa, vinblastine, and capecitabine. Biologics include trastuzumab. Approved treatments include doxorubicin, 5- FU, paclitaxel, docetaxel, gamcitabine, capecitabine and capecitabine plus docetaxel. Specifically, the use of doxorubicin-containing regimens has been associated with higher overall response rates and prolonged time to disease progression as compared to regimens without an anthracycline. However, high cumulative doses of doxorubicin generally must be avoided

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because of the increasing probability of cardiac toxicity with increasing cumulative doses while individual doses are often limited by myelosuppression.

#### **C. Important Milestones in Product Development**

1. Doxil received accelerated approval for the indication of AIDS related refractory Kaposi Sarcoma (November 17, 1995) and refractory advanced ovarian cancer (June 28, 1999).

2. September 23, 2003, the sponsor submitted reports of studies I97-38, C/I96-352, 30-58 and 30-21 for under the IND 36778-N357 (Table 1: Trials submitted for this sNDA review.).

3. October 16, 2003, NDA supplement N50718-SE8-019 which contains the proposed label change was submitted.

4. The sponsor presented efficacy and safety data of Doxil versus doxorubicin as first line therapy in metastatic breast cancer from study I97-328, and proposed an indication for Doxil in metastatic breast cancer as first line therapy in Oct 29th, 2003 EOP-2 meeting. In addition, the sponsor also presented histology data of cardiac biopsy in cancer patients who exposed to anthracycline. Pending review, the FDA disagree with the sponsor on the following:

a) Non-inferiority of Doxil to doxorubicin with respect to PFS was not demonstrated at the dose and schedule evaluated. In addition, the overall response rate was only 9% and 11% for Doxil and doxorubicin, respectively. Objective response data were missing for 33% of subjects treated with Doxil and for 28% of subjects on the comparator arm. Therefore, the relevance of any difference in cardiac toxicity between the two study arms is not clear.

b) The relevance of the biopsy data to clinical cardiac toxicity risk is not clear, especially given the concerns above.

#### **D. Other Relevant Information**

Doxil has been approved for treatment of AIDS related Kaposi Sarcoma (AIDS-KS) and advanced ovarian carcinoma relapsed from a first line platinum containing regimen in the US. Doxil is approved for treatment of AIDS-KS, breast cancer, and ovarian cancer in Canada, Europe, South and Central America, the Middle East, and Asia.

#### **E. Important Issues with Pharmacologically Related Agents**

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Doxil is doxorubicin HCl liposomal formulated injection. The safety information regarding cardiac toxicity is detailed in section VI.C.

## **II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews**

See chemistry review

## **III. Human Pharmacokinetics and Pharmacodynamics**

### **A. Pharmacokinetics**

See previous NDA PK review. No PK review was conducted for this supplemental NDA, as there were no new data submitted.

### **B. Pharmacodynamics**

No animal pharmacology and toxicology review was conducted for this supplemental NDA as there were no new data submitted.

## **IV. Description of Clinical Data and Sources**

### **A. Overall Data**

NDA submission 50-718, October, 2003  
IND submission 36778, N-357, September 25, 2003

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### B. Tables Listing the Clinical Trials

**Table 3: Submitted clinical trials.**

Study Protocol No.	Title
197-328	A Randomized Phase 3 Trial of CAELYX™/ Doxil (SCH 200746) vs. Doxorubicin for the First- Line Treatment of Women with Metastatic Breast Cancer
196-352	A Randomized Multicenter Trial of CAELYX/DOXIL (SCH 200746) as Monotherapy vs. a Comparative Salvage Regimen for the Treatment of Subjects With Advanced Breast Cancer who have Failed a Prior Taxane Containing Regimen
30-58	Assessment of Cardiotoxicity by Endomyocardial Biopsy in Patients with Advanced Malignancies Treated with DOXIL/CAELYX (doxorubicin HCl liposome injection).
30-21	Assessment of Cardiotoxicity by Endomyocardial Biopsy in Patients Receiving Greater than 400 mg/m <sup>2</sup> of DOXIL.

### C. Postmarketing Experience

No information was provided in this supplemental NDA.

### D. Literature Review

The sponsor did not provide a literature review in this supplemental NDA. The reviewer's literature review is as follows:

A'Hern RP, Smith IE, Ebbs SR et al: Chemotherapy and survival in advanced breast cancer: The inclusion of doxorubicin in Cooper type regimens. BRJC 67:801-805, 1993.

Brito RA, Valero V, Buzar AU et al., Long-term results of combined modality therapy for locally advanced breast cancer with ipsilateral supraclavicular metastasis: the University of Texas M.D. Anderson Cancer Center experience. JCO 19:628-633, 2001.

Burstein HJ, Kuter I, Campos SM et al., Clinical activity of trastuzumab and vinorelbine in women with Her2 overexpression metastatic breast cancer. JCO 19:2722-2730, 2001.

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Goss PE and Strasser K, Aromatase inhibitors in the treatment and prevention of breast cancer. JCO 19:881-894, 2001.

Green MC, Buzdar AU, Smith T, et al., Weekly paclitaxel followed by FAC as primary systemic chemotherapy of operable breast cancer improves pathologic complete remission rates when compared to every 3-week paclitaxel therapy followed by FAC-Final results of a prospective phase II randomized trial (Abstract) Proc. Am Soc. Clin Oncol 21:35a, 2002.

Hainsworth JD, Burris HA, Yardley DA et al: Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: a minie pearl cancer research network phase II trial. JCO 19:3500-3505, 2001.

Howell A, Robertson JFR, Quaresma AJ et al: Fulvestrant, formally ICI182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. JCO 20:3396-3403, 2002.

Loesch D, Robert N, Asmar L, et al: Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer. JCO 20: 3857-3864, 2002.

Mackey JR, Paterson A, Dirix LY, et al: Final results of the phase III randomized trial comparing docetaxel, doxorubicin, and cyclophosphamide to FAC as first-line chemotherapy for patients with metastatic breast cancer (abstract). Proc Am Soc Clin Oncol 21:35a, 2002.

O'Shaughnessy J, Miles D, Vukelja S, et al: Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. JCO 20:2812-2823, 2002.

Sledge G, Neuberg D, Bernardo P, et al: Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An intergroup trial (E1193). JCO 21: 588-592.

## V. Clinical Review Methods

### A. How the Review was Conducted

The safety data and the biopsy data were reviewed based on the report of the paper submission.

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#### **B. Overview of Materials Consulted in Review**

Paper documentation of both NDA 50-718 SE8-019, containing proposed label change only, and IND 36778N-357, containing reports of studies I97-328, I96-352, 30-58, and 30-21, were reviewed.

#### **C. Overview of Methods Used to Evaluate Data Quality and Integrity**

The proposed label change, study reports and relevant data sets were carefully reviewed and independent analysis was conducted by the reviewers.

On on-site inspection was not requested.

#### **D. Were Trials Conducted in Accordance with Accepted Ethical Standards**

All four trials were conducted in accordance with accepted ethical standards.

#### **E. Evaluation of Financial Disclosure**

This supplemental NDA dose not contain any financial disclosure. The sponsor has provided the following explanation for the lack of financial disclosure of the four studies:

Study I97-328 was conducted by Schering-Plough from 1998-2001. This study was conducted outside the US and financial disclosure information was not collected.

Schering-Plough conducted the CI96-352 study and indicted that they did not collect financial disclosure information, although there are a few US sites.

The 30-58 study was conducted at 2 sites and the sponsor ALZA did not collect financial disclosure information because of the nature and the size of the study.

The 30-21 study was conducted and completed in 1996 so this would not have collected any financial disclosure information.

### **VI. Integrated Review of Efficacy and Safety**

#### **A. Brief Statement of Conclusions**

Review was focused on safety (see below).

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#### B. General Approach to Review of the Efficacy of the Drug

Review was focused on safety.

#### C. Detailed Review of Trials by Indication

**I. Title: A Randomized Phase 3 Trial of CAELYX™/ Doxil (SCH 200746) vs. Doxorubicin for the First- Line Treatment of Women with Metastatic Breast Cancer  
Protocol No. I97-328**

**Table 4: Protocol Milestones for I97-328**

Date	Landmark events
June 24, 1998	Opening of the trial
September 4, 1998	Amendment 1, administrative, clarified several study procedures.
October 1, 1999	Amendment 2, administrative, further clarification of study procedures.
February 13, 2001	Amendment 3: Changed two interim analysis to one and added cardiac toxicity by cumulative anthracycline as part of event free survival analysis.
July 26, 2001	Study cut off date.
December, 2001	End of survival follow up
Jan 14, 2002	Final report

**Primary endpoint:** to demonstrate that Doxil was non-inferior to doxorubicin with respect to progression-free survival (PFS) and superior to doxorubicin with respect to cardiac safety.

**Secondary endpoints:** overall survival (OS), objective response, tolerability, and health related quality of life (HQL).

**Study design:** This is a randomized, open-label, multicenter (68), comparative study of Doxil versus Doxorubicin in the first line treatment of patients with metastatic breast cancer who received less than 300 mg/m<sup>2</sup> adjuvant doxorubicin. Randomization was 1: 1 between the two treatment regimens. Subjects were stratified prior to randomization according to the following predefined prognostic factors: previous anthracycline therapy (yes/no), presence of bone metastases only (yes/no) and presence of a cardiac risk factor (yes/no) resulting in 8 different strata.

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**Treatment Plan:** Testing regimen is Doxil 50 mg/m<sup>2</sup> every 4 weeks by IV infusion. Reference Therapy is doxorubicin 60 mg/m<sup>2</sup> every 3 weeks. Either treatment continued until disease progression or unacceptable toxicity.

#### Eligibility:

##### Inclusion criteria:

- women  $\geq$  18 years old with measurable or evaluable (CT scan of chest, abdomen or MRI and bone scan) metastatic breast cancer with prior histological or cytological diagnosis;
- performance status  $\leq$  2 (WHO);
- prior hormonal therapy, adjuvant anthracycline therapy (with dose limitations up to 300 mg/m<sup>2</sup> and drug free interval > 12 months), and bisphosphonate use at study entry (for subjects for whom bone was not the only disease site) were permitted;
- Normal hematologic, renal and hepatic function; normal cardiac function (LVEF  $\geq$  lower limit of normal for the institution).
- Measurable or evaluable disease.
- Bisphosphonate is allowed
- Contraception required for child bearing age women.
- Written consent

##### Exclusion criteria:

- Prior chemotherapy for metastatic disease
- Prior adjuvant anthracycline therapy with a cumulative doxorubicin or doxorubicin-equivalent dose exceeding 300 mg/m<sup>2</sup> or a cumulative Epirubicin dose > 450 mg/m<sup>2</sup>.

*Reviewer comment: doxorubicin-equivalent dose is defined as the cumulative dose of any anthracycline except epirubicin.*

- XRT < 3 weeks
- Symptomatic heart disease, history of ischemic heart disease, or LVEF below the range of normal.
- Symptomatic CNS metastasis.
- Pregnancy and lactation.
- Second malignancy < 3 years
- uncontrolled systemic infection

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- concomitant investigational agent

#### Statistical Methods

The study was designed to demonstrate that

(1) Doxil was non-inferior to doxorubicin with regard to PFS (i.e., the lower boundary of the 95% confidence interval [CI] for the hazard ratio [HR] for doxorubicin relative to Doxil was greater than 0.8, where a HR greater than 1 favors Doxil),

(2) To demonstrate that Doxil was superior to doxorubicin with regard to cardiac toxicity ( $p < 0.0499$  for the comparison of cardiac event rates as a function of cumulative lifetime anthracycline dose) for the ITT population.

The primary analysis for PFS, cardiac toxicity and OS were adjusted for strata differences. The effect of other prognostic factors was examined for PFS and OS using Cox's proportional hazards model. Overall response (i.e., the best response was either a CR or a PR) and the duration of response (time between the first date of response to the date of progression) were tabulated and summarized using descriptive statistics. HQL was assessed using the EORTC QLQ-C30. Quality adjusted survival was calculated using the Q-TWiST method. The study was completed per protocol with 509 subjects randomized and 410 events.

#### Drug exposure:

The majority of subjects in both groups received treatment at the intended dose and schedule; 91% of Doxil cycles and 93% of doxorubicin cycles were administered at  $\geq 80\%$  of the protocol-specified dose. Mean dose per cycle was  $48.3 \text{ mg/m}^2$  for Doxil, and  $58.0 \text{ mg/m}^2$  for doxorubicin. Mean cycle length was 29.6 days for Doxil, and 22.3 days for doxorubicin.

*Note: The protocol used q 4 week Doxil at  $50 \text{ mg/m}^2$  whereas doxorubicin was given at  $60 \text{ mg/m}^2$  q 3 week, even though the approved dose of Doxil for ovarian carcinoma and AIDS-KS is either q 3 or q 4 week IV at  $50 \text{ mg/m}^2$ . Because the dose selection of Doxil for this study, the mean dose of Doxil is lower and the cycle length is longer than that of doxorubicin. This suggests that patients on the Doxil arm may have received less total dose and less intensity of the agent. Comparative PK analysis may be helpful to verify this possibility but was not addressed in this study. Therefore, the clinical finding has to be interpreted in light of the difference in dose intensity of the two arms and lack of PK data. Thus, whether Doxil has equal or less cardiac toxicity has not been established*

#### Efficacy:

Although there is no efficacy claim submitted in this supplemental NDA, the sponsor has reported their full study report. According to the sponsor, approximately 60% of the patients had visceral disease, 30% had more than 2

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metastatic sites and approximately half had at least one cardiac risk factor at study entry. PFS was Summarized as follows:

**Table 5: Sponsor’s PFS Analysis in Study I97-328**

	N	censored	Progressed <sup>a</sup>	Median PFS (months)	p-value <sup>b</sup>	HR	95% CI for HR <sup>c</sup>
Doxil	254	52	202	6.9	0.99	1.00	0.82-1.22
Doxorubicin	255	47	208	7.8			
a. Death within 4 months of last tumor evaluation indicating no progression is considered events. b. Stratified log rank test to test superiority of Doxil to doxorubicin. The protocol defined corresponding nominal significant level for final analysis was 0.0499 ( $\alpha$ ). c. Adjusted for the interim analysis (95.01 % CI provided).							

The sponsor claims that the protocol-specified objective of demonstrating that Doxil was non-inferior to doxorubicin was met; the treatment HR adjusted for prognostic variables (HR= 0.99; 95% CI 0.81-1.20) also demonstrated that Doxil was non-inferior to doxorubicin with respect to PFS.

The sponsor also claimed that OS was comparable (HR= 0.94, 95% CI 0.74 - 1.19). Overall response rate (complete + partial) for subjects with measurable disease was 33% with Doxil and 38% with doxorubicin. Results of the Q-TWiST analysis show that there were no utility scenarios under which either drug was significantly better than the other.

*Note: The protocol defined that Doxil may be superior in cardiac toxicity and non-inferior in efficacy to doxorubicin in breast cancer. The sponsor mixed two different event measurements, the cardiac toxicity and the disease progression for PFS analysis. The result of this mixed analysis is difficult to interpret. FDA’s position is that the confidence of comparable efficacy in PFS and survival in this particular disease setting was not established. Further more, the sponsor is not making any efficacy claim in the proposed label revisions.*

**Safety:**

The sponsor has included cardiac toxicity as a PFS event in the primary analysis. The sponsor’s primary analysis of cardiac toxicity is shown in

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Table 6: Analysis of first cardiac event.

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**Table 6: Analysis of first cardiac event in study I97-328**

	Doxil N = 254	Doxorubicin N = 225	P value, HR (95% CI)
Patients who developed cardiotoxicity (LVEF defined)	10	48	<0.001 3.16 (1.58-6.31)
Cardotoxicity with signs and symptoms of CHF	0	10	-
Cardotoxicity with no signs and symptoms of CHF	10	38	-
Patients WITH signs and symptoms of CHF only	2	2	-

The sponsor indicated that a total of 58 (10 Doxil, 48 doxorubicin) subjects had LVEF-defined cardiac toxicity. None of the Doxil subjects but 10 of 48 doxorubicin subjects who had LVEF-defined cardiac toxicity also had signs and symptoms of CHF. At cumulative doses > 450 mg/m<sup>2</sup>, the risk of cardiotoxicity for Doxil subjects did not increase; whereas, with doxorubicin the risk continued to increase with the cumulative dose. For Doxil subjects the mean % decrease in LVEF remained at approximately 2-3% regardless of cumulative dose. In contrast, for doxorubicin subjects, the mean% decrease in LVEF was positively correlated with cumulative anthracycline dose.

*Note: Study I97-328 did not sufficiently demonstrate that Doxil replacement for doxorubicin would provide a reduction in the cardiac toxic effects if doxorubicin was used. Some methodological issues that arose during the review include the apparent disparity in cumulative anthracycline dose between the two arms and disparities in the frequency of cardiac evaluation between the two arms. The difference of LVEF assessment schedule on each treatment arm and variations of cumulative dose of anthracycline among patients may introduce bias to the interpretation of the study result. In addition, the clinical concern of this toxicity comparison is that the comparable efficacy of the two agents in this disease setting has not been established.*

*Therefore, the comparative data proposed for the label suggesting of reduced toxicity, potentially providing further impetus for replacement of doxorubicin by Doxil in clinical situations where doxorubicin is of established benefit and in which Doxil has no known benefit. There are two dimensions to the public health risk represented by allowing the comparative data to be included into the label. Potentially reduced benefit resulting in shortened survival and presumed reduction in toxicity which does not exist or if it exists, is not of the magnitude claimed in the study I97-328. Thus, FDA suggests inclusion of Doxil safety data alone without a direct comparison to doxorubicin in the label.*

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*In fact, the sponsor did not request a new indication or a new efficacy claim due to the recognition on their part that results from study I97-328 do not constitute adequate evidence of comparable efficacy. In a precedent experience, FDA denied approval of another liposomal doxorubicin product despite the conduct of two large randomized studies, due to lack of confidence that the efficacy of the new formulation has not been compromised by the drug formulation. (see letter to the editor, Williams et al. Developing Drugs to Decrease the Toxicity of Chemotherapy, JCO )*

Of the most frequent treatment-related AEs, alopecia (20% vs 66%), nausea (37% vs 53%) and vomiting (19% vs 31%) were less common with Doxil than with doxorubicin. Neutropenia was less common with Doxil (4% vs 10%) and less severe. Pronounced or total hair loss was 7% with Doxil and 54% with doxorubicin. PPE was reported in 48% of Doxil subjects; 17% was grade 3, 0% was grade 4 and only 7% discontinued due to PPE. Infusion reactions occurred in 13% of Doxil subjects; most were mild to moderate and did not limit treatment; 84% of subjects were successfully rechallenged and tolerated treatment for 2-14 additional cycles. Four (2%) Doxil subjects discontinued due to severe allergic reactions. Discontinuations due to AEs were 24% with Doxil and 11% with doxorubicin, the difference predominantly due to PPE. When cardiotoxicity was considered in conjunction with other AEs, discontinuation rates were virtually identical. Doxil was slightly less myelosuppressive than doxorubicin with respect to anemia and leukopenia. Both treatments had similar minimal effects on liver and renal function.

*Note: Although the sponsor is claiming that Doxil produces less cardiac AEs, there were more treatment discontinuations due to AE in Doxil arm (24%) than in the doxorubicin arm(11%).*

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**II. Study Title: A Randomized Multicenter Trial of CAELYX/DOXIL(SCH 200746) as Monotherapy vs. a Comparative Salvage Regimen for the Treatment of Subjects With Advanced Breast Cancer who have Failed a Prior Taxane Containing Regimen  
Protocol No. I96-352**

**Table 7: Protocol Milestones for Study I96-352**

June 23, 1997	Trial started
June 27, 1997	Amendment 1: Change of control arm dosing regimen and define tumor measurement criteria
December 17, 1997	Amendment 2: removing epirubicin as a comparator choice.
June 9, 1998	Amendment 3: redefined clinical best response and tumor staging.
April 1, 1999	Cut off date

**Primary endpoint:** to compare progression-free survival of Doxil to standard salvage chemotherapy.

**Secondary Endpoints:**

- a) overall response rate;
- b) response duration;
- c) overall survival;
- d) event- free survival;
- e) tolerability;
- f) Clinical benefit response and health-related quality of life.

**Study design:** This is a randomized, controlled, open-label, parallel group, multicenter (52) trial. Subjects with advanced breast cancer who had failed a prior taxane-containing regimen were randomized to receive Doxil or standard salvage therapy (Navelbine or mitomycin C + vinblastine). Comparator selection by site was investigator-determined at the time of site initiation. Subjects were stratified prior to randomization based on the number of prior chemotherapy regimens for metastatic disease (1 vs. 2) and whether they had bone metastases only. Study drug or comparator was administered until the occurrence of unacceptable toxicity or disease

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### **Eligibility:**

#### Major criteria for Inclusion:

- Histological proof of breast cancer and radiographic evidence of metastatic or locally advanced breast cancer - Stages IIIB and IV.
- At least 1 measurable or evaluable lesion. (Subjects with bone lesions only could have been included).
- At least 1, but no more than 2, prior chemotherapy regimens for advanced disease (excluding adjuvant therapy).
- The last regimen must have included Taxol or Taxotere.
- No more than 2 months could have intervened from demonstration of taxane failure to study (Taxane failure was defined as having progressed while on a taxane-containing regimen or progressed within 6 months of the last dose of a taxane-containing regimen).
- Subjects with prior bone marrow transplant or stem cell rescue were included.
- Females  $\geq 18$  years.
- Women of child-bearing potential had to have a pregnancy test to demonstrate that they were not pregnant and were to practice appropriate birth control throughout the entire course of this study.
- Stable Karnofsky performance status  $\geq 60\%$ .
- LVEF greater than or equal to the lower limit of normal for the institution.
- Completion of the Baseline Health-Related Quality of Life Questionnaire.
- Written informed consent must have been signed and dated.

#### Major criteria for exclusion:

- pregnancy or lactation
- second malignancy
- significant medical or psychiatric illness
- Platelet  $< 100,000/\text{ul}$ , ANC  $< 1500/\text{ul}$ , or Hb  $< 9 \text{ g/dl}$ .
- Serum Creatinine  $> 1.5 \text{ ULN}$ .
- ALT, AST or bilirubin  $> 2 \text{ x ULN}$  (4 x ULN in case of liver metastasis).
- Experimental agent exposure  $< 4$  weeks.
- Prior anthracycline therapy with a cumulative doxorubicin-equivalent dose  $> 450 \text{ mg/m}^2$ , or a cumulative epirubicine dose  $> 840 \text{ mg/m}^2$ .

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- NYHA class II or higher cardiac disease.
- Uncontrolled systemic infection.
- Prior Doxil exposure
- XRT < 3 weeks
- CNS metastatic disease.

**Treatment:** Testing arm is using Doxil 50 mg/m<sup>2</sup> IV every 4 weeks. Study drug was administered until the occurrence of unacceptable toxicity or progression. Control arm could be one of the following: Navelbine: 30 mg/m<sup>2</sup> IV once a week; mitomycin C + vinblastine: mitomycin C 10 mg/ m<sup>2</sup> IV infusion on Day 1 and vinblastine 5 mg/m<sup>2</sup> IV infusion on Days 1 and 21 in 6-8 week cycles.

**Criteria for Evaluation:** All clinical safety assessments were to be performed every 4 weeks except hematology data were to be assessed weekly. LVEF by MUGA scan and Tumor measurement were to be assessed every 8 weeks.

The primary efficacy variable was progression-free survival objectively assessed every 8 weeks in both treatment groups. Secondary efficacy variables were overall response rate, response overall survival, event-free survival, tolerability, clinical benefit response and health-related quality of life, Adverse events and laboratory tests were evaluated for safety.

### Statistical Methods

- The study was originally designed to show superiority of Doxil vs the active comparator with regard to progression free survival (50% improvement in PFS, i.e., HR= 1.5, a HR value > 1.0 favors Doxil).
- For progression- free survival, the protocol specified a target of 250 subjects and 225 events. The study was completed per protocol with 301 subjects randomized and 246 events.
- All analyses were performed on the intent to treat population using a 5% level of significance (2- sided).
- Baseline demographic and disease characteristics were compared between treatment groups.
- The Kaplan-Meier method and stratified log rank test were used for the primary efficacy variable, progression free survival, overall survival and event-free survival.
- The Q-TWiST method and clinical benefit response were used for health-related quality of life.

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#### **Efficacy:**

There were 301 subjects randomized: 150 to receive Doxil and 151 to receive the comparator (Navelbine or mitomycin C + vinblastine). The mean cycle length with Doxil was 29.8 days and the mean cycle dose for Doxil was 48.6 mg/m<sup>2</sup>.

The median age for this study population was 56.0 years; most subjects were Caucasian (85%) women who had stage IV disease (96%) and a visceral site of metastasis (64%). Approximately 40% of the study population had primary anthracycline resistant breast cancer.

The sponsor's analyses are as follows:

(1) PFS was similar for Doxil and the active comparator, with a strong trend favoring Doxil (HR= 1.26, 95% CI 0.98- 1.62, p= 0.11, median PFS 2.9 months vs. 2.5 months), albeit not reaching statistical significance. The PFS data were mature with 246 events representing 82% of the total study population. .

(2) Overall survival was longer for Doxil than for the comparator (HR= 1.07, 95% CI 0.79-1.45, p= 0.57, median overall survival 10.4 months vs. 9.0 months). As of the clinical cut-off for the report (April 1, 1999), there were 172 events (subject deaths) representing 56% of the total study population. An updated mature survival analysis (October 2001) with 90% of the subject deaths having occurred, demonstrated that the original overall survival trend in favor of Doxil was maintained (HR= 1.05; 95% CI 0.82-1.33, p= 0.71, median 11.0 months vs. 9.0 months).

**Reviewer note:** *The reviewer did not examine the efficacy result of this study, since the proposed label changes do not include any efficacy claim.*

#### **Safety:**

Per sponsor's analysis, the most frequently reported AEs common to all 3 groups (Doxil, Navelbine and mitomycin C + vinblastine, respectively) were nausea (31%, 27%, and 23%), vomiting (20%, 17%, and 18%) and fatigue/asthenia (20%/ 9%, 21%/ 15%, 9%/ 32%).

The most common treatment-related AE with Doxil was palmar plantar erythema / hand foot syndrome (PPE/HFS, 37%); which was completely reversible with dose modification. The incidence of Grade 3 PPE was 18% and there was only 1 case of Grade 4 PPE. The discontinuation rate due to PPE was 8%.

The incidences of neuropathy (11% vs. 1%), constipation (16% vs. 5%) and pain (13% vs. 4%) were higher with Navelbine compared with Doxil.

The incidence of alopecia was low in both the Doxil and Navelbine groups (3% and 5%).

Overall, the safety profile of Doxil with respect to myelosuppression was superior when compared with Navelbine or mitomycin C + vinblastine. Grade 3/4

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decreases in leukocytes were 54% with Navelbine and 30% with mitomycin C + vinblastine compared to 20% with Doxil. Grade 3/4 neutropenia was also more common with Navelbine than with Doxil (8% vs 2%). There were 2 Navelbine subjects but no Doxil subjects who developed concomitant fever and neutropenia.

**Reviewer note:** *The reviewer agrees with the sponsor's analysis and concurs that adding detailed grading and management for PPE in the Doxil label is appropriate.*

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#### **III. Study Title: Assessment of Cardiotoxicity by Endomyocardial Biopsy in Patients with Advanced Malignancies Treated with Doxil/CAELYX (doxorubicin HCl liposome injection).**

**Protocol No.** 30-58

#### **Objectives:**

- 1) To make a histological assessment of the effect of Doxil for patients who have received a cumulative doxorubicin-equivalent of  $\geq 550 \text{ mg/m}^2$  (including Doxil) or  $\geq 400 \text{ mg/m}^2$  of Doxil alone.
- 2) To determine the potential risk of individual patients continuing Doxil therapy beyond  $400 \text{ mg/m}^2$ .

**Primary Endpoint:** Endomyocardial biopsy score. Biopsy scores were measured using the Morphologic Grading System for Cardiotoxicity, a grading system developed by Billingham & Bristow (1984). According to this grading system, scores range from Grade 0 (normal myocardial ultrasound morphology) to Grade 3.0 (severe and diffuse myocyte damage affected by vacuolization and/or myofibrillar loss).

**Reviewer note:** *The clinical relevance of the cardiac histology grading system has not been established.*

#### **Study design:**

This was a prospective investigation (2 centers) of patients receiving Doxil alone or in combination with other chemotherapeutic drugs to define the cardiac biopsy findings in individuals receiving a cumulative doxorubicin-equivalent dose of  $\geq 550 \text{ mg/m}^2$  (including Doxil) or  $\geq 400 \text{ mg/m}^2$  of Doxil alone. It was anticipated that a minimum of 15 patients would be studied to determine the histologic and functional effects of Doxil therapy. Patients with advanced malignancies were enrolled in the study.

**Reviewer note:** *The rationale of chosen different cumulative dose of Doxil versus doxorubicin (including Doxil) is not clear.*

Prior to the biopsy procedure, patients had a pre-endomyocardial biopsy evaluation that included an assessment of potential risk factors for doxorubicin-induced cardiac toxicity, a left ventricular radionuclide ejection, and an electrocardiogram (ECG). All tests were to be obtained within 14 days of the endomyocardial biopsy.

Patients underwent a right ventricular endomyocardial biopsy. An approach through the right internal jugular vein or the right femoral vein was used. The

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biopsies were performed by experienced personnel at [REDACTED] (b) (4)

[REDACTED]. At least three pieces of the myocardium were obtained from each patient and fixed in a glutaraldehyde/paraformaldehyde buffer. Enough cardiac tissue was taken to prepare ten blocks per patient for electron microscopy.

All specimens were evaluated at a pathology laboratory at [REDACTED] (b) (4). The biopsies were graded utilizing the scale and grading system developed by Dr. Billingham et al (Billingham & Bristow 1984).

No study drugs were administered in this study.

#### **Eligibility:**

Major criteria for Inclusion:

- Received a cumulative doxorubicin-equivalent dose of  $\geq 550$  mg/m<sup>2</sup> (including Doxil or  $\geq 400$  mg/m<sup>2</sup> of Doxil alone).
- Histologic and/or clinical evidence of distantly metastatic, locally advanced, or recurrent malignancy.
- Able to travel to sites where biopsies were to be performed.
- Platelet count  $>100,000$ /mm<sup>3</sup>, and hemoglobin  $\geq 10$  g/dL (may be augmented with transfusions).
- Prothrombin time (PT) and partialthromboplastin time (PTT) had to within normal limits.
- Written informed consent obtained.

Exclusion criteria:

- Signs and symptoms of active opportunistic infection.
- Life expectancy was less than 3 months.
- Patient was pregnant or lactating.
- Patient was physically, mentally, or emotionally unable to give informed consent.
- Patient had a history of hemophilia or systemic anticoagulation disorder or other medical status that deemed the patient ineligible for the procedure.
- Patient had intracardiac shunt lesions.

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- Patient had known hypersensitivity to Valium or other medications needed for the procedure.

#### **Treatment:**

No study drugs were administered in this study. However, patients could be concurrently enrolled in a SEQUUS-sponsored clinical trial utilizing Doxil or could be receiving Doxil as a commercial agent.

#### **Assessments**

**Table 8: Assessment Schedule for Study 30-38**

	Pre-endomyocardial Biopsy Evaluation <sup>f</sup>	Cardiac Evaluation
Medical History	X	
Physical Examination	X	
Performance status determination	X	
Assessment of potential risk factors for doxorubicin-induced cardiac toxicity <sup>a</sup>	X	
Complete blood count (CBC) with differential	X	
Chemistry Profile 16 <sup>b</sup> , prothrombintime (PT), partial thromboplastintime (PTT), creatin ephosphokinase (CPK), Lactatedehydroqenase(LDH)	X	
Left ventricular radionuclide ejection	X	
Electrocardiogram (ECG)	X	X <sup>g</sup>
Record all medications patient currently receiving	X	
Cardiac functional status <sup>c</sup>		X <sup>g</sup>
Chest X-ray (posteroanterior and lateral)		X <sup>g</sup>
Echocardiogram (performed at primary research site) or radionuclide cardiac ejection fraction		X <sup>g</sup>
CPK with isoenzymes if elevated		X <sup>g</sup>
LDH with cardiac isoenzymes if elevated		X <sup>g</sup>
Endomyocardial biopsy <sup>d</sup>		X
Endomyocardial biopsy grading <sup>e</sup>		X

a. Cumulative doxorubicin dose, cumulative anthracycline dose (including Doxil), prior chest irradiation, history of coronary artery disease, hypertension, age, and previous history of heart disease, e.g., valvular.

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b Total protein, albumin, calcium, phosphate, glucose, uric acid, total bilirubin, alkaline phosphatase, aspartate amino transferase (AST), amino alanine transferase (AL T), sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, and creatinine.

c. detailed in the protocol.

d Performed according to the methods standard for each experienced site. Examples of the procedures are presented in the study protocol.

e Performed using the Morphologic Grading System for Cardiotoxicity (Billingham et al1978). This system is outlined in the study protocol.

f To be performed prior to study entry.

g To be completed prior to the endomyocardial biopsy.

### **Statistics**

A minimum of 15 evaluable patients was to be enrolled. The sample size was based on clinical judgement rather than on statistical concerns.

*Reviewer note: The sample size was determined without consideration of statistical power.*

### **Patient disposition**

A total of 8 patients with advanced malignancies were enrolled at the two study sites between September1997 and October 2000. The first patient received her biopsy on September19, 1997and the last patient received her biopsy on October 26, 2000. The protocol anticipated a minimum of 15 patients; however, only 8 patients were enrolled due to difficult patient accrual. A total of ten biopsies were performed, eight at the UK site and two at the Stanford site. Two patients had two biopsies each (see table below).

**Reviewer note:** *The protocol closed due to slow enrollment. Only50% of planned accrual was fulfilled.*

### **Demographics and Baseline Characteristics**

Seven (87.5%) patients were female and one (12.5%) was male. All (100%) patients were white and ranged in age from 35 to 66 years. Five patients had breast cancer, two had ovarian cancer, and one had AIDS-related Kaposi's sarcoma.

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**Table 9: Cardiac Biopsy Results for Study 30-38**

Patient ID No.	Cumulative Doxorubicin Dose (mg/m <sup>2</sup> )	Cumulative Doxil Dose (mg/m <sup>2</sup> )	Total anthracycline (mg/m <sup>2</sup> )	Biopsy Score*
042006	0	730	730	0.0
042012 <sup>a</sup>	375	592	967	0.0
	375	952	1327	0.0
359001 <sup>a, b</sup>	360	900	967	1.5
042015	360	1320	1327	1.5
042036	360	490	850	1.5
042053	0	685	685	0.0
042058	180	564	744	0.5
146001	0	1485	1485	1.0
359002	0	498	498	1.0

a Second biopsy obtained about one year after the first biopsy.

b Patient IDs 359001 and 042015 correspond to the same person.

\* The cardiac biopsy scores ranging, from Grade 0 to 1.5, indicated minimal damage to the cardiac cells.

**Reviewer note:**

*We consider study 30-58 to be exploratory. Due to limited sample size (8 patients) and variable prior therapy (with or without prior doxorubicin, the cumulative dose of doxorubicin and Doxil), no conclusions can be reached on whether there is a difference in the cardiac effect of Doxil vs. doxorubicin, or on safety of Doxil beyond any limit of doxorubicin, or on the relevance of the biopsy data to clinical cardiac toxicity risk. These data should not be included in the Doxil label since they would not provide any meaningful guidance for clinical practice in the use of Doxil.*

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#### **IV. Assessment of Cardiotoxicity by Endomyocardial Biopsy in Patients Receiving Greater than 400 mg/m<sup>2</sup> of Doxil Protocol No. 30-21**

##### **Objectives:**

- 1) To make a histological assessment of the effect of Doxil on myocardial structure in patients who have received Doxil in a cumulative dose of > 400 mg/m<sup>2</sup>.
- 2) To compare myocardial biopsy scores after cumulative Doxil administration to a historical database of patients who have received standard nonliposomal doxorubicin.
- 3) To determine the potential risk to individual patients of continuing Doxil therapy above 400 mg/m<sup>2</sup>.

**Study design:** Ten patients with AIDS-related Kaposi's sarcoma (KS) who had received Doxil in cumulative doses ranging from 469 to 860 mg/m<sup>2</sup> underwent myocardial biopsy. For each Doxil patient, a matched doxorubicin patient who had received a similar cumulative amount of doxorubicin was identified from a cardiac biopsy database. Using a 7-point morphological grading system for cardiotoxicity, the amount of cardiac damage in the Doxil and doxorubicin patients was measured and compared. Blinded reading of pathology specimens was used

##### **Doxil exposure:**

Doxil at 20 mg/m<sup>2</sup> every two to three weeks intravenous infusions or nonliposomal doxorubicin at a dose intensity of 20 mg/m<sup>2</sup> per week on one of two schedules: 20 mg/m<sup>2</sup> every week or 60 mg/m<sup>2</sup> every three weeks (intravenous infusions over 15 minutes).

##### **Eligibility:**

Major criteria for Inclusion:

Doxil patients:

- Patient had received a cumulative dose of > 400 mg/ m<sup>2</sup> of Doxil.
- Patient had not received anthracycline therapy other than Doxil.
- Patient's platelet count > 100,000/mm<sup>3</sup>, Hgb > 10 gm/dL.
- Patient's PT and PTT were within normal limits.

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Doxorubicin historical control group:

For each of the ten Doxil patients enrolled in the study, a matched control patient was identified from a database of 131 patients who had undergone cardiac biopsy while participating in clinical trials of doxorubicin at Stanford University from 1974-1982. The primary criterion for a match was cumulative doxorubicin exposure within:  $\pm 10 \text{ mg/m}^2$ .

#### Criteria for evaluation:

The primary criterion for evaluation was the condition of the myocardium as assessed by the Billingham Morphologic Grading System for Cardiotoxicity. This scale begins at Grade 0 (cells show no anthracycline damage) and progresses to Grade 3.0 (specimens exhibit diffuse cell damage, with more than 35% of cells showing pathologic change, loss of contractile elements and organelles, and mitochondrial and nuclear degeneration).

#### Cardiac biopsy scores:

**Table 10: Sponsor's Summary of Cardiac Biopsy Scores of Study 30-21**

	Doxil	Doxorubicin – Administered Dose Unadjusted	Doxorubicin- Administered Dose Adjusted
Mean ( $\pm$ SD)	0.5 ( $\pm$ 0.55)	2.4 ( $\pm$ 0.70)	1.8 ( $\pm$ 0.78)
Median	0.3 (range 0 - 1.5)	2.8 ( range 1.5 - 3.0)	2.2 ( range 0.7 - 3.0)

\* The difference between the Doxil and doxorubicin patients was statistically significant. The p-value was  $< 0.001$  when the biopsy scores for the Doxil patients were compared with the unadjusted scores for the doxorubicin patients. The same test comparing the Doxil patient scores with the doxorubicin patient scores adjusted for administered dose also gave a significant difference ( $p = 0.015$ ). Cardiac biopsy scores in ten patients treated with Doxil in cumulative doses ranging from 469 - 860  $\text{mg/m}^2$  show significantly less myocardial damage than found in control patients having received similar or less cumulative doses of standard doxorubicin.

**Reviewer note:** *The use of historical control and the use of a very small sample size (10) make the clinical significance of the study results questionable.*

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### D. Efficacy and Safety Conclusions:

There was no efficacy claim proposed for this sNDA. The main safety findings were as follows:

1) Regarding cardiac toxicity, the data describing Doxil exposure and toxicity is acceptable. The comparative cardiac toxicity of Doxil versus doxorubicin should not be included in the Doxil label because the following:

a) the efficacy of Doxil in the first line setting of metastatic breast cancer in comparison to doxorubicin has not been established.

b) The differences in anthracycline dose intensity and in the frequency of cardiac assessment between the two arms may have introduced bias in the cardiac toxicity findings in favor of Doxil.

2) The cardiac biopsy study data are considered exploratory and the relevant clinical significance is questionable.

(3) The two comparative studies (I97-328 and I96-352) also indicated that Doxil is associated with increased incidences of hand foot syndrome/palmar plantar erythema (HFS/PPE), infusions reactions and mucositis/stomatitis.

## VII. Drug Exposure and Toxicity

### A. Brief Statement of Conclusions

A total of 404 patients with metastatic breast cancer were exposed to Doxil in studies I97-328 (N=254) and I96-352 (N=150). No comparative conclusions regarding cardiac toxicity of Doxil versus doxorubicin can be draw from the study I97-328. Significant hand foot syndrome / palmar platar erythema (HFS/PPE) was observed on the Doxil arm in study I96-352.

### B. Description of Patient Exposure

**Table 11: Sponsor's summary of Drug exposure in studies I97-328 and I96-352**

Study	Treatment	N	Intend dose and schedule (5)	Mean dose per cycle (mg/m <sup>2</sup> )	Mean cycle length (days)
I97-328	Doxil	254	91%	48.3	29.6
	doxorubicin	255	93%	58.0	22.3
I96-352	Doxil	150	83	48.6	29.8
	other	151	54.7	-	-

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The sponsor's primary analysis of cardiac toxicity in study I97-328 is shown in

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Table 6: Analysis of first cardiac event. The frequent toxicities due to Doxil treatment observed on studies I97-328 and I96-352 are summarized as follows:

**Table 12: The Reviewer’s analysis of Adverse Events related to Doxil in Studies I97-328 and I96-352**

Adverse Events	I97-328 (%)	P value	I96-352 (%)	P value
Alopecia	20#	0.0001	3	-
Fatigue	12	-	20	-
Nausea	37#	0.042	31	-
Vomiting	19#	0.002	20	-
Mucositis NOS	23*	0.002	14*	0.0001
Stomatitis	22*	0.02	22*	0.0001
Neutropenia	4	-	20#	0.004
PPE	48*	0.0001	37*	0.0001
Grade 3	17		18	
Grade 4	0		1	
Discontinued	7		8	
Infusion reaction	13*	0.0001	12*	0.023
Discontinuation due to AE	24*	0.0001	19	-

# Statistically significant less than the control arm by the Fisher’s exact test.

\* Statistically significant more than the control arm by the Fisher’s exact test.

- No statistical significance.

**Reviewer note:** *The reviewer agreed with the sponsor to add detailed grading for PPE and management for both PPE and infusion reaction to Doxil label. Based on the two studies toxicity profiles, the sponsor should consider to point out that Doxil has higher incidences of mucositis and stomatitis comparing to doxorubicin, Navelbine, and mitomycin+Vinblastine. Although the incidences of nausea and vomiting is much less for Doxil treatment comparing to that of doxorubicin, the incidence of AE caused treatment discontinuation were much higher in Doxil arm than that of doxorubicin arm.*

### C. Methods and Specific Findings of Safety Review

## CLINICAL REVIEW

### Clinical Review Section

The data set provided in this supplemental NDA was reviewed by the guide line of CTC criteria (see above for review).

**D. Adequacy of Safety Testing**

See above.

**E. Summary of Critical Safety Findings and Limitations of Data**

The data from two comparative studies indicated that Doxil has more frequent PPE, mucositis/stomatitis, and infusion reaction. The comparative data regarding reduced cardiac toxicity, nausea and vomiting on Doxil exposure versus doxorubicin exposure would require further clinical study to confirm.

### **VIII. Dosing, Regimen, and Administration Issues**

None

### **IX. Use in Special Populations**

**A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation**

Not applicable

**B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

Not applicable

**C. Evaluation of Pediatric Program**

Not applicable

**D. Comments on Data Available or Needed in Other Populations**

None

# CLINICAL REVIEW

## Clinical Review Section

### **X. Conclusions and Recommendations**

#### **A. Conclusions**

- 1) No efficacy claim is requested for this sNDA.
- 2) Regarding cardiac toxicity, the data describing Doxil exposure and toxicity is acceptable. The comparative cardiac toxicity of Doxil versus doxorubicin should not be included in the Doxil label for the following reasons: (i) the efficacy of Doxil in the first line setting of metastatic breast cancer in comparison to doxorubicin has not been established. (ii) The differences in anthracycline dose intensity and in the frequency of cardiac assessment between the two arms may have introduced bias in the cardiac toxicity findings in favor of Doxil.
- 3) The cardiac biopsy study data are considered exploratory and the relevant clinical significance is questionable.
- 4) The two comparative studies (I97-328 and I96-352) also indicated that Doxil is associated with increased incidences of hand foot syndrome/palmar plantar erythema (HFS/PPE), infusions reactions and mucositis/stomatitis.

#### **B. Recommendations**

The DODP, CDER, USFDA recommends approval of the supplemental NDA application with the following revisions to the sponsor proposed label based on data from studies in metastatic breast cancer and cancer patients previously exposed to anthracyclines:

1. The Doxil label revision should only include data of Doxil exposure and toxicity, but should not include the comparative cardiac toxicity data for doxorubicin.
2. The label revisions regarding dosing or administration guidelines of palmar plantar erythema (PPE), mucositis and infusion reactions are acceptable.
3. The cardiac biopsy data are exploratory and should not be included in the label.

### **XI. Appendix**

#### **A. Other Relevant Materials**

None

## CLINICAL REVIEW

### Clinical Review Section

**B. Individual More Detailed Study Reviews (If performed)**

None

APPEARS THIS WAY ON ORIGINAL

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this page is the manifestation of the electronic signature.**  
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/s/

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Qin Ryan  
10/22/04 06:46:42 PM  
MEDICAL OFFICER

Ramzi Dagher  
10/25/04 09:03:20 AM  
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**50-718/S-019**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

EXCLUSIVITY SUMMARY for NDA # 50-718 SUPPL # 019

Trade Name DOXIL® Generic Name doxorubicin HCl liposome injection

Applicant Name Alza Corporation HFD-150

Approval Date October 27, 2004

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/\_\_\_/ NO /X/

b) Is it an effectiveness supplement? YES /X/ NO /\_\_\_/

If yes, what type(SE1, SE2, etc.)? SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /X/ NO /\_\_\_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /\_\_\_/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /X/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /X/ NO /\_\_\_/

If yes, NDA # 50-718

Drug Name Doxil®

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /\_\_\_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_\_/ NO /\_\_\_/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_\_\_/                      NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/                      NO /\_\_\_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/                      NO /\_\_\_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_\_\_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /\_\_\_/ NO /\_\_\_/

Investigation #2 YES /\_\_\_/ NO /\_\_\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/

Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # H3E-MC-JMEI

Investigation #2, Study # H3E-MC-JMBR

Investigation #\_\_, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
!  
IND # YES /\_\_\_/ ! NO /\_\_\_/ Explain:  
!  
!  
!  
!  
!  
  
Investigation #2 !  
!  
IND # YES /\_\_\_/ ! NO /\_\_\_/ Explain:  
!  
!  
!  
!  
!  
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
!  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
!  
\_\_\_\_\_  
!  
\_\_\_\_\_  
!  
!  
  
Investigation #2 !  
!  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
!  
\_\_\_\_\_  
!  
\_\_\_\_\_  
!  
!  
!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/                      NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Patty Garvey , R.Ph.  
Regulatory Project Manager

Date

\_\_\_\_\_  
Richard Pazdur, M.D.  
Director  
Division of Oncology Drug Product

Date

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-610/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

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Richard Pazdur  
10/27/04 03:41:06 PM

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA <b>50-718</b>	Efficacy Supplement Type <b>SE-8</b>	Supplement Number <b>019</b>
Drug: <b>DOXIL® (doxorubicin HCl liposome injection)</b>		Applicant: <b>Alza Corporation</b>
RPM: <b>Patty Garvey, R.Ph.</b>		HFD- <b>150</b> Phone # <b>301-594-05766</b>
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
<b>❖ Application Classifications:</b>		
<ul style="list-style-type: none"> <li>• Review priority</li> </ul>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<ul style="list-style-type: none"> <li>• Chem class (NDAs only)</li> </ul>		
<ul style="list-style-type: none"> <li>• Other (e.g., orphan, OTC)</li> </ul>		<b>Not Applicable</b>
<b>❖ User Fee Goal Dates</b>		
		<b>October 29, 2004</b>
<b>❖ Special programs (indicate all that apply)</b>		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
<b>❖ User Fee Information</b>		
<ul style="list-style-type: none"> <li>• User Fee</li> </ul>		<input checked="" type="checkbox"/> Paid
<ul style="list-style-type: none"> <li>• User Fee waiver</li> </ul>		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
<ul style="list-style-type: none"> <li>• User Fee exception</li> </ul>		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
<b>❖ Application Integrity Policy (AIP)</b>		
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP</li> </ul>		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• Exception for review (Center Director's memo)</li> </ul>		<b>Not Applicable</b>
<ul style="list-style-type: none"> <li>• OC clearance for approval</li> </ul>		<b>Not Applicable</b>
<b>❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification &amp; certifications from foreign applicants are cosigned by US agent.</b>		
		<input type="checkbox"/> Verified - <b>Not Applicable</b>
<b>❖ Patent</b>		
<ul style="list-style-type: none"> <li>• Information: Verify that form FDA-3542a was submitted.</li> </ul>		<input type="checkbox"/> Verified - <b>Not Applicable</b>
<ul style="list-style-type: none"> <li>• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.</li> </ul>		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).</li> </ul>		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>Exclusivity summary</li> </ul>	<b>October 27, 2004</b>
<ul style="list-style-type: none"> <li>Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!</i></li> </ul>	( ) Yes, Application # _____ ( <b>X</b> ) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	<b>Not Applicable</b>
<b>General Information</b>	
❖ Actions	
<ul style="list-style-type: none"> <li>Proposed action</li> </ul>	( <b>X</b> ) AP ( ) TA ( ) AE ( ) NA
<ul style="list-style-type: none"> <li>Previous actions (specify type and date for each action taken)</li> </ul>	<b>Not Applicable</b>
<ul style="list-style-type: none"> <li>Status of advertising (approvals only)</li> </ul>	( <b>X</b> ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> <li>Press Office notified of action (approval only)</li> </ul>	( ) Yes ( <b>X</b> ) Not applicable
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	( <b>X</b> ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter ( ) Other
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> <li>Division's proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	<b>Included in package</b>
<ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>	<b>Not Applicable</b>
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<b>October 28, 2004</b>
<ul style="list-style-type: none"> <li>Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)</li> </ul>	<b>Not Applicable</b>
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	<b>Not Applicable</b>
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> <li>Division proposed (only if generated after latest applicant submission)</li> </ul>	<b>Not Applicable</b>
<ul style="list-style-type: none"> <li>Applicant proposed</li> </ul>	<b>Not Applicable</b>
<ul style="list-style-type: none"> <li>Reviews</li> </ul>	<b>Not Applicable</b>
❖ Post-marketing commitments	
<ul style="list-style-type: none"> <li>Agency request for post-marketing commitments</li> </ul>	<b>Not Applicable</b>
<ul style="list-style-type: none"> <li>Documentation of discussions and/or agreements relating to post-marketing commitments</li> </ul>	<b>Not Applicable</b>
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	<b>Included in package</b>
❖ Memoranda and Telecons	<b>Included in package</b>
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>EOP2 meeting (indicate date)</li> </ul>	<b>Not Applicable</b>
<ul style="list-style-type: none"> <li>Pre-NDA meeting (indicate date)</li> </ul>	<b>Not Applicable</b>
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (indicate date; approvals only)</li> </ul>	<b>Not Applicable</b>
<ul style="list-style-type: none"> <li>Other</li> </ul>	

❖ Advisory Committee Meeting	
• Date of Meeting	<b>Not Applicable</b>
• 48-hour alert	<b>Not Applicable</b>
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	<b>Not Applicable</b>
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) ( <i>indicate date for each review</i> )	<b>Not Applicable</b>
<b>Clinical Information</b>	
❖ Clinical review(s) ( <i>indicate date for each review</i> )	<b>October 25, 2004</b>
❖ Microbiology (efficacy) review(s) ( <i>indicate date for each review</i> )	<b>Not Applicable</b>
❖ Safety Update review(s) ( <i>indicate date or location if incorporated in another review</i> )	<b>Not Applicable</b>
❖ Risk Management Plan review(s) ( <i>indicate date/location if incorporated in another rev</i> )	<b>Not Applicable</b>
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	<b>Not Applicable for SE-8</b>
❖ Statistical review(s) ( <i>indicate date for each review</i> )	<b>Not Applicable</b>
❖ Biopharmaceutical review(s) ( <i>indicate date for each review</i> )	<b>Not Applicable</b>
❖ Controlled Substance Staff review(s) and recommendation for scheduling ( <i>indicate date for each review</i> )	<b>Not Applicable</b>
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	<b>Not Applicable</b>
• Bioequivalence studies	<b>Not Applicable</b>
<b>CMC Information</b>	
❖ CMC review(s) ( <i>indicate date for each review</i> )	<b>Not Applicable</b>
❖ Environmental Assessment	
• Categorical Exclusion ( <i>indicate review date</i> )	<b>Not Applicable</b>
• Review & FONSI ( <i>indicate date of review</i> )	<b>Not Applicable</b>
• Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	<b>Not Applicable</b>
❖ Microbiology (validation of sterilization & product sterility) review(s) ( <i>indicate date for each review</i> )	<b>Not Applicable</b>
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<b>Not Applicable</b>
❖ Nonclinical inspection review summary	<b>Not Applicable</b>
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<b>Not Applicable</b>
❖ CAC/ECAC report	<b>Not Applicable</b>

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/s/

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Patricia Garvey  
10/28/04 07:41:45 AM

## REGULATORY PROJECT MANAGER REVIEW

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**NDA:** 50-718 /S-019

**Drug:** Doxil® (doxorubicin HCl liposome injection)

**Applicant:** ALZA Corporation

**Submission Dates:** October 16, 2004  
October 28, 2004

**Receipt Dates:** December 29, 2003  
October 29, 2003

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### **BACKGROUND:**

This supplemental new drug application provides significant changes to the following sections of the product labeling – **BOX WARNING, WARNINGS, PRECAUTIONS (Information for the Patient), DOSAGE AND ADMINISTRATION (AIDS-KS Patients, Dose Modifications and Preparation for Intravenous Administration)**. The reference to “Doxil” has been changed “DOXIL” throughout the package insert. Also minor editorial changes were made to provide additional guidance to prescribing physicians.

This supplement was submitted on October 16, 2003 however an unacceptable for filing letter was issued on November 4, 2003. This letter was issued because the appropriate user fee was not received. The appropriate user fee was received on December 29, 2003 which also triggered the start of the PFUDA goal date.

In addition, the Division of Oncology Drug Products approved supplement 010 on January 10, 2002, which provided for proposed changes to conform to recommendations made in our January 31, 2001 approval letter. In addition, item 2 in the Boxed Warnings and Infusion Reactions subsection, under the WARNINGS section, have been strengthened based on a review of post-marketing reports.

On August 5, 2003, the sponsor submitted the supplement 010 Final Printed Labeling (FPL) and this was acknowledged and retained on March 18, 2004. However, the sponsor had also submitted a supplement 010 FPL on March 28, 2002, which has not been reviewed, acknowledged or retained.

### **DOCUMENT REVIEWED:**

I compared the October 29, 2003 labeling submission to the August 5, 2003 FPL for S-010, which was acknowledged and retained on March 18, 2004. Supplement 010 was approved on January 10, 2002.

**REVIEW:**

1. The following minor editorial and addition were made throughout the package insert.

- a. The proprietary name of “Doxil” was changed to capital “DOXIL”.

This change was reviewed by the chemistry team leader, Dr. Nallaperumal Chidambaram, and found acceptable.

- b. The change for the establish name from “(doxorubicin HCl liposome injection)” to (doxorubicin HCl) (b) (4) liposome injection”.

This change was reviewed by the chemist, Dr. Xiao Chen, and found unacceptable because it is promotional in nature, and is also against current thinking within the Agency for liposome drug product.

This was conveyed to the sponsor on October 4, 2004 and the sponsor agreed with the Dr. Chen’s decision.

2. In the BOX WARNING section, WARNING #1 was revised based on data from Study I97-328 and text added text to provide guidance to the physician in regards to the cardiac toxicity risk for Doxil based upon completed Phase 3 study.

1. Experience with Doxil in (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/m<sup>2</sup>. 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.

Changed to:

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<sup>2</sup>. 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<sup>2</sup> every 4 weeks. At all cumulative anthracycline doses between 450 – 500 mg/m<sup>2</sup> or between 550 – 550 mg/m<sup>2</sup>, the risk of cardiac toxicity for patients treated with

DOXIL® was 11%. Prior use of other anthracyclines or anthracenedione 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**).

The sponsor and the medical officer, Dr. Qin Ryan, worked together on the revisions and had come to a final agreement with the above changes.

3. Under the CLINICAL PHARMACOLOGY section, Pharmacokinetics subsection, the word “related” was added to the heading of the table as followed:

“Pharmacokinetic Parameters of DOXIL® in Patients with AIDS-related Kaposi’s Sarcoma”

The addition was reviewed by the medical officer, Dr. Qin Ryan, and found acceptable.

4. The CLINICAL PHARMACOLOGY section, Clinical Studies subsection, the following changes were made.
  - a. Under the Ovarian Cancer section, the following addition was added to the second paragraph.

“The baseline demographics and clinical characteristics of the patients with refractory ovarian cancer are provided in the following table.”

- b. Under the Ovarian Cancer section, the following addition was made to the heading of the tables.

“Patient Demographics for Patients with Refractory Ovarian Cancer from Phase 2 Ovarian Cancer Studies”

“Response Rates in Patients with Refractory Ovarian Cancer from Single Arm Ovarian Cancer Studies”

- c. Under the Indicator Lesion Assessment section, the following addition was made to the heading of the table.

“Response in Patients with Refractory<sup>a</sup> AIDS-KS”

These changes were reviewed by the medical officer, Dr. Qin Ryan, and found acceptable.

5. The INDICATIONS AND USAGE section, WARNINGS section, under the Cardiac Toxicity subsection.

- a. The following first paragraph was deleted.

[REDACTED] (b) (4)

- b. The following second paragraph was revised to provide guidance to prescribing physician based on the I97-328 study.

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/m<sup>2</sup>.

Changed to:

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 doxorubicin of dosage exceeding the currently recommended limit of 550 mg/m<sup>2</sup>.

- c. The following second sentence of the third paragraph, the word “and” was deleted and “anthracycline” was added.

“Congestive heart failure ~~and~~/or cardiomyopathy may be encountered after discontinuation of anthracycline therapy.”

- d. The following addition was made to third and fourth sentences of the fourth paragraph.

“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®.”

These changes were reviewed by the medical officer, Dr. Qin Ryan, and found acceptable.

- e. The last paragraph was deleted upon the recommendation of the medical officer, Dr. Qin Ryan. This was acceptable to the sponsor.

[REDACTED] (b) (4)

- f. The following paragraph and table were added at the end of the Cardiac Toxicity section.

“In a large clinical study in patients with advanced breast cancer, 250 patients received DOXIL® at starting dose of 50mg/m<sup>2</sup> every 4 weeks. At all cumulative anthracycline doses between 450 – 500 mg/m<sup>2</sup> or between 500-550 mg/m<sup>2</sup>, the risk of cardiac toxicity for patients treated with DOXIL® was 11%. In this study, cardiotoxicity was defined as a decrease of  $\geq 20\%$  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**).”

**Number of Patients**

	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 & symptoms of CHF only	2

“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.”

The sponsor and the medical officer, Dr. Ryan Qin, worked together on the revisions and had come to a final agreement with the above changes.

6. The INDICATIONS AND USAGE section, WARNINGS section, under the Myelosuppression subsection.
- a. The following phrase “with relapsed” was added in the first sentence of the first and second paragraph.

“In patients with relapsed ovarian cancer, myelosuppression ...”

“In patients with relapsed ovarian cancer, 3.3% ...”

- b. In the third paragraph the words “for” and “with” were added.

“For patients with AIDS-KS, who often ...”

These additions were reviewed by the medical officer, Dr. Qin Ryan, and found acceptable.

7. The INDICATIONS AND USAGE section, WARNINGS section, under the Infusion Reaction subsection. The word “with” was added to the last sentence of the first paragraph.

“Acute infusion-related reactions ... Six patients with AIDS-KS (0.9%) and 13 (1.7%) patients ...”

The addition was reviewed by the medical officer, Dr. Qin Ryan, and found acceptable.

8. The INDICATIONS AND USAGE section, WARNINGS section, the Palmar-Plantar Erythrodysesthesia subsection was replaced with “Hand-Foot Syndrome (HFS).”

Therefore, from this point on in the package insert “Palmar-Plantar Erythrodysesthesia” and “PPE” were replaced with “Hand-Foot Syndrome” and “HFS”. Also, the word “with” was added to the first sentence of this subsection.

“In patients with ovarian cancer patients, 37.4% of ...”

These changes were reviewed by the medical officer, Dr. Qin Ryan, and found acceptable.

9. The PRECAUTIONS section, Information for the Patients section, the following paragraph was added at the end of the section to provide guidance and clarity to the physician and patient.

“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.”

This addition was reviewed by the medical officer, Dr. Qin Ryan, and found acceptable.

10. The ADVERSE REACTIONS section, the word “with” was added to several headings and tables of this section.

“Patients with Ovarian Cancer”

“Hematology Data Reported in Patients with Ovarian Cancer”

“Patients with AIDS-KS”

“Hematology Data Reported in Patients with AIDS-KS”

“Patients with Refractory or Intolerant AIDS-KS (n = 74)”

“Total Patients with AIDS-KS (n = 720)”

“Probably and Possibly Drug-Related Non-Hematologic Adverse Events  
Reported in  $\geq$  5% of Patients with AIDS-KS”

“The following additional (not in table) adverse events were observed in patients  
with AIDS-KS; ...”

These additions were reviewed by the medical officer, Dr. Qin Ryan, and found acceptable.

11. The following changes were made to the DOSAGE AND ADMINISTRATION section.

- a. The subsection “Ovarian Cancer Patients” changed to “Patients with Ovarian Cancer.”
- b. Under the AIDS-KS Patients subsection, the following text added after the first sentence to guide healthcare practitioners on drug administration.

“DOXIL® (doxorubicin HCl liposome injection) should be ... 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, ...”

- c. The following changes were under the Dose Modification Guidelines subsection.
  - i. The table heading “Palmar-Plantar Erythrodysesthesia(PPE) was replace with “Hand Foot Syndrome (HFS)”.
  - ii. “HFS” was added after “Redose unless patients has experience previous Grade 3 or 4 HFS” under the #1 Dose Adjustment heading of the Hand Foot Syndrome table. This is to clarify dose reductions for toxicity specific for HFS.
  - iii. The word “stomatitis” was added after “Redose unless patients has experience previous Grade 3 or 4 stomatitis” under the #1 Dose Adjustment heading of the STOMATITIS table. This is to clarify dose reductions for toxicity specific for stomatitis.
  - iv. Under the #2 Dose Adjustment heading of the Hand Foot Syndrome table, the following text was added to provide guidance to the physician for retreatment of patients who experienced Grade 2 toxicity and who had previous Grade 3-4 toxicity.

“If resolved to Grade 0-1 within 2 weeks, and there was no prior Grade 3-4 HFS, continue treatment at previous dose and return to original treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.”

- v. Under the #2 Dose Adjustment heading of the STOMATITIS table, the following text was added to provide guidance to the physician for retreatment of patients who experienced Grade 2 toxicity and who had previous Grade 3-4 toxicity.

“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 treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.”

- vi. Under the Preparation for Intravenous Administration subsection, the following text was added to guide healthcare practitioners on dilution of product prior to administration after the first sentence.

“Doses exceeding 90 mg should be diluted in 500 mL of 5% Dextrose Injection, USP prior to administration.”

- vii. Under the Preparation for Intravenous Administration subsection, the following sentence was added for guidance for drug administration at the end of the subsection.

“Rapid flushing of the infusion line should be avoided.”

The following above changes were reviewed by the medical officer, Dr. Qin Ryan, and found acceptable.

12. It was recommended to the sponsor that the REFERENCES section be revised to the following references as per the Division’s policy.

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, MA 02115.
5. Clinical Oncological 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 J 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-SystPharm*. 1996;53-1669-1685

The sponsor agreed with this recommendation.

**RECOMMENDED REGULATORY ACTION:**

This supplement 010 FPL submission dated March 28, 2004 should be acknowledged and retained.

It is the policy of the Office of Drug Evaluation I and the Division of Oncology Drug Products to include only those references which pertain to the handling of antineoplastic agents. Therefore, in the **REFERENCES** section, the sponsor will be requested to revise their references appropriately.

With the concurrence of the medical officer and chemistry reviewer, this supplement 019 should be approved.

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Patty Garvey, R.Ph.  
Regulatory Project Manager

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Dotti Pease  
Chief, Project Management Staff

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Patricia Garvey  
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Dotti Pease  
10/27/04 09:23:06 AM  
CSO

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

**To:** Brian Maloney, R.Ph. – J&JPRD

**From:** Patty Garvey, R.Ph.

**Fax:** 908-722-5113

**Fax:** (301) 594-0498

**Phone:** 908-927-2228

**Phone:** (301) 594-5766

**Pages (including cover):** 1

**Date:** August 9, 2004

**Re:** sNDA 50-718/s-019 Doxil

**Urgent**    **For Review**    **Please Comment**    **Please Reply**    **Please Recycle**

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● **Comments:**

Brian,

Please refer to your sNDA 50-718/s-019 Doxil. The following is a request from the clinical reviewer.

In the process of reviewing your NDA 50718 supplement SE8-019, we noticed that in your IND 36778 N-357 submission, Vol1, page 62, regarding the study I97-328, stated "Pharmacokinetics has been addressed in the previous submission". For understanding the justification of the dose and schedule difference between the Doxil and doxorubicin regimens in the study I97—328, we would like to see your comparative PK analysis of Doxil and doxorubicin. If you have submitted such data, please provide a brief summary with ID of the previous submission which contains the comparative PK analysis. If you have such data but has not submitted, please submit them under sNDA 50-718/s019.

Please contact me if you have any questions.

Sincerely,

Patty Garvey  
Project Manager  
Division of Oncology Drug Products

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Patricia Garvey  
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CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 50-718/S-019

Johnson & Johnson Pharmaceutical Research & Development, LLC  
Attention: Brian Maloney, R.Ph.  
Associate Director, Regulatory Affairs  
920 Route 202 South, P.O. Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

This letter supercedes the filing communication letter dated February 26, 2004. The February 26, 2004 letter had reference the incorrect submission date of October 28, 2004. This correct date should be October 28, 2003.

Please refer to your October 16, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DOXIL® (doxorubicin HCl liposome injection).

We also refer to your submission dated October 28, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 27, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,

*{See appended electronic signature page}*

Dotti Pease  
Chief, Project Management Staff  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 50-718/S-019

Johnson & Johnson Pharmaceutical Research & Development, LLC  
Attention: Brian Maloney, R.Ph.  
Associate Director, Regulatory Affairs  
920 Route 202 South, P.O. Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

Please refer to your October 16, 2003 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DOXIL® (doxorubicin HCl liposome injection).

We also refer to your submission dated October 28, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 27, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,

*{See appended electronic signature page}*

Dotti Pease  
Chief, Project Management Staff  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Patricia Garvey  
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Signed for Dotti Pease



NDA 50-718/S-019

**PRIOR APPROVAL SUPPLEMENT**

Johnson & Johnson Pharmaceutical Research & Development, LLC  
Attention: Brian Maloney, R.Ph.  
Associate Director, Regulatory Affairs  
920 Route 202 South, P.O. Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: DOXIL® (doxorubicin HCl liposome injection)  
NDA Number: 50-718  
Supplement number: 019  
Review Priority Classification: Standard (S)  
Date of supplement: October 16, 2003  
Date of receipt: December 29, 2003

This supplemental application proposes the following changes: significant changes to the following sections of the product labeling – **BOX WARNING, WARNINGS, PRECAUTIONS (Information for the Patient), DOSAGE AND ADMINISTRATION (AIDS-KS Patients, Dose Modifications and Preparation for Intravenous Administration)**. The reference to “Doxil” has been changed “DOXIL” throughout the package insert. Also minor editorial changes were made to provide additional guidance to prescribing physicians.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 27, 2004 in accordance with 21 CFR 314.101( a). If the application is filed, the user fee goal date will be October 29, 2004.

Under 21 CFR 314.102(c), you may request an informal conference with this Division ( to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Document Room  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and research  
Division of Oncology Drug Products, HFD-150  
Attention: Document Room 3067  
1451 Rockville Pike  
Rockville, Maryland 20852

If you have any question, call Patty Garvey, Regulatory Project Manager, at (301) 594-5766.

Sincerely,

*{See appended electronic signature page}*

Dotti Pease  
Chief, Project Management Staff  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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Patricia Garvey  
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Signed for Dotti Pease



NDA 50-718/S-019

Johnson & Johnson Pharmaceutical Research & Development, LLC  
Attention: Brian J Maloney, R.Ph.  
Associate Director, Regulatory Affairs  
920 Route 202 South  
P.O. Box 300  
Raritan, NJ 08869

Dear Mr. Maloney:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Doxil® (doxorubicin HCl liposome injection)

NDA Number: 50-718

Supplement Number: 019

Date of Application: October 16, 2003

Date of Receipt: October 17, 2003

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration  
P.O. Box 360909  
Pittsburgh, PA 15251-6909

Checks sent by a courier should be addressed to:

Food and Drug Administration (360909)  
Mellon Client Service Center, Room 670  
500 Ross Street  
Pittsburgh, PA 15262-0001

**NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.**

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Division Document Room, 3067  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Division Document Room, 3067  
1451 Rockville Pike  
Rockville, Maryland 20852

If you have any questions, call Patty Garvey, Regulatory Project Manager, at 301-594-5766.

Sincerely,

*{See appended electronic signature page}*

Dotti Pease  
Chief, Project Management Staff  
Division of Oncology Drug Products  
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