CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 50-718/S-006

Trade Name:	DOXIL
Generic or Proper Name:	doxorubicin HCl liposome injection
Sponsor:	ALZA Corporation
Approval Date:	June 28, 1999
Indication:	Doxil (doxorubicin HCl liposome injection) is indicated for: 1. The treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory disease is defined as disease that has progressed while on treatment, or within 6 months of completing treatment. 2. The treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy. 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 50-718/S-006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-718/S-006

APPROVAL LETTER

NDA 50-718/S-006

ALZA Corporation
Attention: Janne Wissel
Sr. Vice President, Operations
950 Page Mill Road
P.O. Box 10950
Palo Alto, CA 94303-0802

Dear Ms. Wissel:

Please refer to your supplemental new drug application dated December 23, 1998, received December 29, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Doxil® (doxorubicin HCl liposome injection).

We acknowledge receipt of your submissions dated January 27, February 11 and 24, March 3 and 31, April 20 and 22, June 17, 21, and 25, 1999.

This supplemental new drug application provides for the use of Doxil (doxorubicin HCl liposome injection) for 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.

We have completed the review of this supplemental application, as amended, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve Doxil (doxorubicin HCl liposome injection) for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved under 21 CFR Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations.

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

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten 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-006." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study 30-49 entitled, "A Phase 3, Randomized, Open-Label, Comparative Study of Doxil/CAELYX versus Topotecan HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy" and your commitments agreed upon in your submission dated June 25, 1999. These commitments, along with the completion dates agreed upon, are listed below.

> You agree to provide data from the interim analysis of study 30-49 by July 12, 1999, and the final study analysis by the week of March 31, 2000.
>
> If after review and discussion of the data with you, we believe that the results demonstrate convincing superiority of Doxil over topotecan HCl in either time to progression (TTP) or survival, with a supporting trend demonstrated for the other endpoint, then this would likely fulfill the Phase 4 requirement for demonstrating clinical benefit. In that case, you agree to submit a supplemental NDA within 6 months.
>
> If the results of study 30-49 do not demonstrate the clinical benefit of Doxil, you agree to submit a protocol for a study designed to prove the clinical benefit of Doxil in ovarian cancer and a proposed timetable for completion and submission of the study. The protocol and timetable will be submitted within one month of the meeting with the Agency at which the results of this study are discussed.

Final study reports should be submitted to this NDA as a supplemental application. For administrative purposes, all submissions relating to this Phase 4 commitment must be clearly designated "Subpart H Phase 4 Commitments."

In addition, we note your following Phase 4 commitment, specified in your submission dated June 25, 1999, that is not a condition of the accelerated approval. This commitment provides for:

> Submission of complete clinical pharmacokinetic data for verification by the Agency and incorporation into the package insert, as appropriate. This data should be submitted within 45 days of the action letter date.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Alvis Dunson, Project Manager, at (301) 594-5750.

Sincerely,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-718/S-006

LABELING

Doxil®

[*däk'sil*]

(**doxorubicin HCl liposome injection)**

FOR INTRAVENOUS INFUSION ONLY

A product of ALZA Pharmaceuticals

A division of ALZA Corporation

Palo Alto, CA 94303 USA

WARNINGS

1. Experience with Doxil® (doxorubicin HCl liposome injection) at high cumulative doses is too limited to have established its effects on the myocardium. It should therefore be assumed that Doxil® will have myocardial toxicity similar to conventional formulations of doxorubicin HCl. Irreversible myocardial toxicity leading to congestive heart failure often unresponsive to cardiac supportive therapy may be encountered as the total dosage of doxorubicin HCl approaches 550 mg/m^2. Prior use of other anthracyclines or anthracenediones will reduce the total dose of doxorubicin HCl that can be given without cardiac toxicity. Cardiac toxicity also may occur at lower cumulative doses in patients with prior mediastinal irradiation or who are receiving concurrent cyclophosphamide therapy.

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

2. Acute infusion-associated reactions (flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest or throat, and/or hypotension) have occurred in about 5% to 10% of patients treated with Doxil®. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction has resolved with slowing of the infusion rate. Doxil® should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions. (See **WARNINGS—Infusion Reactions**.)
3. Severe myelosuppression may occur. (See **WARNINGS—Myelosuppression**.)
4. Dosage should be reduced in patients with impaired hepatic function. (See **DOSAGE AND ADMINISTRATION**.)
5. Accidental substitution of Doxil® for doxorubicin HCl has resulted in severe side effects. Doxil should not be substituted for doxorubicin HCL on a mg per mg basis. **(**See **DESCRIPTION** and **DOSAGE and ADMINISTRATION.)**
6. Doxil® should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

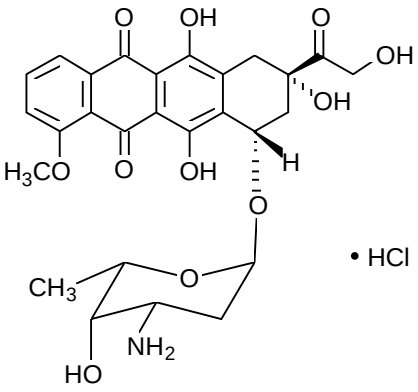
DESCRIPTION

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

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

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

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

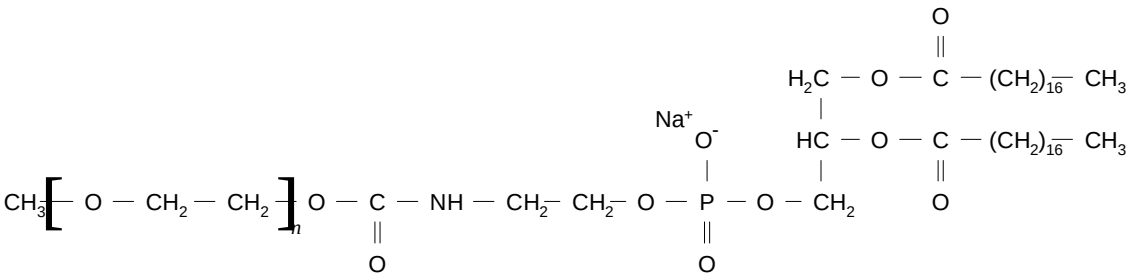


The molecular formula of the drug is $C_{27}H_{29}NO_{11}\cdot HCl$; its molecular weight is 579.99.

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

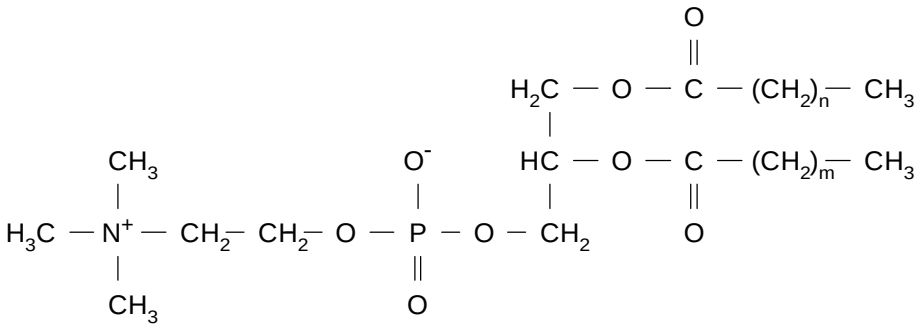
concentration of 2 mg/mL and a pH of 6.5. The STEALTH® liposome carriers are composed of N-(carbonyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each mL also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. Greater than 90% of the drug is encapsulated in the STEALTH® liposomes.

MPEG-DSPE has the following structural formula:



n = ca. 45

HSPC has the following structural formula:



m, n = 14 or 16

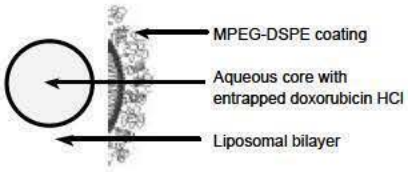
CLINICAL PHARMACOLOGY

Mechanism of Action

The active ingredient of Doxil® is doxorubicin HCl. The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

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

Representation of a STEALTH® liposome:



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

It is hypothesized that because of their small size (ca. 100 nm) and persistence in the circulation, the pegylated Doxil® liposomes are able to penetrate the altered and often compromised vasculature of tumors. This hypothesis is supported by studies using colloidal gold-containing STEALTH® liposomes, which can be visualized microscopically. Evidence of penetration of STEALTH®

liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C-26 colon carcinoma tumors and in transgenic mice with Kaposi's sarcoma-like lesions. Once the STEALTH® liposomes distribute to the tissue compartment, the encapsulated doxorubicin HCl becomes available. The exact mechanism of release is not understood.

Pharmacokinetics

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

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

Parameter (units)	Dose	
	10 mg/m^2	**20 mg/m^2**
Peak Plasma Concentration (μg/mL)	4.12 ± 0.215	8.34 ± 0.49
Plasma Clearance (L/h/m^2)	0.056 ± 0.01	0.041 ± 0.004
Steady State Volume of Distribution (L/m^2)	2.83 ± 0.145	2.72 ± 0.120
AUC (μg/mL•h)	277 ± 32.9	590 ± 58.7
First Phase (λ_1) Half-Life (h)	4.7 ± 1.1	5.2 ± 1.4
Second Phase (λ_2) Half-Life (h)	52.3 ± 5.6	55.0 ± 4.8

N = 23
Mean ± Standard Error

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

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

expected to be more than proportional at a 50 mg/m^2 dose when compared with the lower doses.

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

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

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

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

Special Populations: The pharmacokinetics of Doxil® have not been separately evaluated in women, in members of different ethnic groups, or in individuals with renal or hepatic insufficiency.

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

Tissue Distribution

Kaposi's sarcoma lesions and normal skin biopsies were obtained at 48 and 96 hours postinfusion of 20 mg/m^2 Doxil® in 11 patients. The concentration of Doxil® in KS lesions was a median of 19 (range, 3-53) times higher than in

normal skin at 48 hours posttreatment; however, this was not corrected for likely differences in blood content between KS lesions and normal skin. The corrected ratio may lie between 1 and 22 times. Thus, higher concentrations of Doxil® are delivered to KS lesions than to normal skin.

Clinical Studies

Ovarian Carcinoma

Doxil® (doxorubicin HCl liposome injection) was studied in three open-label, single-arm, clinical trials of 176 patients with metastatic ovarian carcinoma. One hundred forty-six (146) of these patients were refractory to both paclitaxel- and platinum-based chemotherapy regimen. Refractory patients are defined as those having progressive disease while on treatment, or within 6 months of completing treatment. Patients in these studies received Doxil® at 50 mg/m^2 infused over one hour every 3 or 4 weeks for 3-6 cycles or longer in the absence of dose-limiting toxicity or progression of disease.

The baseline demographics and clinical characteristics of the refractory patients are shown in the following table .

Patient Demographics for Refractory Patients from Phase 2 Ovarian Cancer Studies

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

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

The response rates for the individual phase 2 trials are given in the following table:

Response Rates in Refractory Patients from single arm Ovarian Cancer Studies

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

These 77 patients were predominantly white, homosexual males with a median CD4 count of 10 cells/mm^3. Their age ranged from 24 to 54 years, with a mean age of 38 years. Using the ACTG staging criteria,[1] 78% of the patients were at poor risk for tumor burden, 96% at poor risk for immune system, and 58% at poor risk for systemic illness at baseline. Their mean Karnofsky status score was 74%. All 77 patients had cutaneous or subcutaneous lesions, 40% also had oral lesions, 26% pulmonary lesions, and 14% of patients had lesions of the stomach/intestine. The majority of these patients had disease progression on prior systemic combination chemotherapy.

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

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

Investigator Assessment

Investigator response was based on modified ACTG criteria.[1] Partial response was defined as no new lesions, sites of disease, or worsening edema; flattening of ≥ 50% of previously raised lesions or area of indicator lesions decreasing by ≥ 50%; and response lasting at least 21 days with no prior progression.

Indicator Lesion Assessment

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

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

Responses are summarized in the tables below.

Response in Refractory[a] AIDS-KS

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

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

[a] Patients with disease that progressed on prior combination chemotherapy or who were intolerant to such therapy.

[b] There were no complete responses in this population.

INDICATIONS AND USAGE

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

1. The treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory disease is defined as disease that has progressed while on treatment, or within 6 months of completing treatment.
2. The treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.

These indications are based on objective tumor response rates. No results are available from controlled trials that demonstrate a clinical benefit resulting from this treatment, such as improvement in disease-related symptoms or increased survival.

CONTRAINDICATIONS

Doxil® (doxorubicin HCl liposome injection) is contraindicated in patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin HCl or the components of Doxil®.

WARNINGS

Cardiac Toxicity

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

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

Caution should be observed in patients who have received other anthracyclines,and the total dose of doxorubicin HCl given should take into account any previous or concomitant therapy with other anthracyclines or related compounds. Congestive heart failure and/or cardiomyopathy may be encountered after discontinuation of therapy. Patients with a history of cardiovascular disease should be administered Doxil® only when the potential benefit of treatment outweighs the risk.

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

In the AIDS-KS studies, 68 (9.6%) patients experienced cardiac-related adverse events. In 30 patients (4.3%), the event was thought to be possibly or probably related to Doxil®. Nine cases of possibly or probably related cardiomyopathy and/or congestive heart failure were reported. Seven (1.0%) of the possibly or probably related cardiac events were severe. These severe events included arrhythmia (nonspecific), cardiomyopathy, heart failure, pericardial effusion, and tachycardia. Three patients discontinued study due to cardiac events.

Myelosuppression

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

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

In AIDS-KS patients, who often present with baseline myelosuppression due to such factors as their HIV disease or concomitant medications, myelosuppression appears to be the dose-limiting adverse event, even at the recommended dose of 20 mg/m^2. Leukopenia is the most common adverse event (about 60%) experienced in this population; anemia (about 20%) and thrombocytopenia

(about 10%) can also be expected. Sepsis occurred in 5% of patients; for 0.7% of patients the event was considered possibly or probably related to Doxil®. Eleven patients (1.6%) discontinued study because of bone marrow suppression or neutropenia.

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

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

Infusion Reactions

Acute infusion-related reactions, characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness in the chest and throat, and/or hypotension have occurred in 5% to 10% of patients treated with Doxil®. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction resolves when the rate of infusion is slowed. The majority of infusion-related events occurred during the first infusion. Six AIDS-KS patients (0.9%) and 13 (1.7%) solid tumor patients discontinued Doxil® therapy because of infusion-related reactions. Similar reactions have not been reported with conventional doxorubicin and they presumably represent a reaction to the Doxil® liposomes or one of its surface components.

The initial rate of infusion should be 1 mg/min to help minimize the risk of infusion reactions. (See **DOSAGE AND ADMINISTRATION.**)

Palmar-Plantar Erythrodysesthesia

In ovarian cancer patients, 37.4% of patients experienced PPE (developed palmar-plantar skin eruptions characterized by swelling, pain, erythema and, for some patients, desquamation of the skin on the hands and the feet), with 16.4% of the patients reporting Grade 3 or 4 events. Thirteen (3.5%) of the ovarian cancer patients discontinued treatment due to PPE or other skin toxicity. (See definitions of PPE grades in **DOSAGE AND ADMINISTRATION, Dose Modification Guidelines.**)

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

PPE was generally seen after 2 or 3 cycles of treatment but may occur earlier. In most patients the reaction is mild and resolves in one to two weeks so that prolonged delay of therapy need not occur. However, dose modification may be required to manage PPE. (See **DOSAGE AND ADMINISTRATION, Dose Modification Guidelines.**) The reaction can be severe and debilitating in some patients and may require discontinuation of treatment.

Pregnancy Category D

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

There are no adequate and well-controlled studies in pregnant women. If Doxil® is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. If pregnancy occurs in the first few months following treatment with Doxil, the prolonged half-life of the drug must be considered. Women of childbearing potential should be advised to avoid pregnancy.

Toxicity Potentiation

The doxorubicin in Doxil® may potentiate the toxicity of other anticancer

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

Injection Site Effects

Doxil® is not a vesicant, but should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of Doxil®, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. (See **DOSAGE AND ADMINISTRATION.**) If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. **Doxil® must not be given by the intramuscular or subcutaneous route**.

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

Hepatic Impairment

The pharmacokinetics of Doxil® have not been adequately evaluated in patients with hepatic impairment. Doxil® dosage should be reduced in patients with impaired hepatic function. (See **DOSAGE AND ADMINISTRATION**.)

Prior to Doxil® administration, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin. (See **DOSAGE AND ADMINISTRATION**.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

PRECAUTIONS

General

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

Laboratory Tests

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

Drug Interactions

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

doxorubicin HCl.

Pregnancy
Pregnancy Category D: (See **WARNINGS**.)

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

Pediatric Use
The safety and effectiveness of Doxil® in pediatric patients have not been established.

Geriatric Use
Of the 373 ovarian cancer patients, 29% were 60 to 69 years old, while 22.8% were 70 years and over. No overall differences were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out. There are insufficient data for a comparative evaluation of efficacy according to age.

Radiation Therapy
Recall of skin reaction due to prior radiotherapy has occurred with Doxil® administration.

Information for the Patient (See **Patient Package Insert)**
Patients and patients' caregivers should be informed of the expected adverse effects of Doxil®, particularly hand-foot syndrome, stomatitis, and neutropenia and its complications of neutropenic fever, infection, and sepsis.

Hand-Foot Syndrome (Palmar-Plantar Erythrodysesthesia): Patients who experience tingling or burning, redness, flaking, bothersome swelling, small blisters, or small sores on the palms of their hands or soles of their feet

(symptoms of Hand-Foot Syndrome) should notify their physician.

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

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

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

ADVERSE REACTIONS

Ovarian Cancer Patients

Safety data are available from 373 ovarian cancer patients treated with Doxil® in 4 clinical studies. The patient population was predominantly white (93.6%) with a median age of 60 years. Patients received a median cycle dose of 50 mg/m^2 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^2. 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.

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

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

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

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

Incidence 1% to 5%

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

Digestive System: dyspepsia, oral moniliasis, mouth ulceration, esophagitis, dysphagia.
Metabolic and Nutritional System: peripheral edema, dehydration.
Musculoskeletal System: myalgia.
Nervous System: somnolence, dizziness, depression, insomnia, anxiety.
Respiratory System: dyspnea, cough increased, rhinitis.
Cutaneous: pruritus, skin discoloration, skin disorder, vesiculobullous rash, maculopapular rash, exfoliative dermatitis, herpes zoster, sweating.
Special Senses: conjunctivitis, taste perversion.

Incidence Less Than 1%

Body As A Whole: cellulitis, anaphylactoid reaction, ascites, flu syndrome, neck pain, moniliasis, injection site pain, face edema, chills and fever, pelvic pain, chest pain substernal, injection site inflammation.
Cardiovascular System: hypertension, angina pectoris, pericardial effusion, postural hypotension, hypotension, palpitation, syncope, shock, bradycardia, arrhythmia, phlebitis, tachicardia, 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, eccymosis, 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, blepheritis, parosmia, taste loss.
Urogenital System: urinary tract infection, leukorrhea, cystitis, nocturia, dysuria, breast pain, mastitis, oliguria, vaginitis, kidney function abnormal, vaginal hemorrhage, hydronephrosis, vaginal moniliasis.

AIDS-KS Patients

Information on adverse events is based on the experience reported in 753 patients with AIDS-related KS enrolled in four studies. The majority of patients were treated with 20 mg/m^2 of Doxil® (doxorubicin HCl liposome injection) every two to three weeks. The median time on study was 127 days and ranged from 1 to 811 days. The median cumulative dose was 120 mg/m^2 and ranged from 3.3 to 798.6 mg/m^2. Twenty-six patients (3.0%) received cumulative doses of greater than 450 mg/m^2.

Of these 753 patients, 61.2% were considered poor risk for KS tumor burden, 91.5% poor for immune system, and 46.9% for systemic illness; 36.2% were poor risk for all three categories. Patients' median CD4 count was 21.0 cells/mm^3, with 50.8% of patients having less than 50 cells/mm^3. The mean absolute neutrophil count at study entry was approximately 3000 cells/mm^3.

Patients received a variety of potentially myelotoxic drugs in combination with Doxil®. Of the 693 patients with concomitant medication information, 58.7% were on one or more antiretroviral medications; 34.9% patients were on zidovudine (AZT), 20.8% on didanosine (ddI), 16.5% on zalcitabine (ddC), and 9.5% on stavudine (D4T). A total of 85.1% patients were on PCP prophylaxis, most (54.4%) on sulfamethoxazole/ trimethoprim. Eighty-five percent of patients were receiving antifungal medications, primarily fluconazole (75.8%). Seventy-two percent of patients were receiving antivirals, 56.3% acyclovir, 29% ganciclovir, and 16%

foscarnet. In addition, 47.8% patients received colony stimulating factors (sargramostim/ filgrastim) sometime during their course of treatment.

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

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

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

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

	Refractory or Intolerant AIDS-KS Patients	Total AIDS-KS Patients
Number of Patients	77	705
Number of Patients Reporting Adverse Events	57 (74.0%)	586 (83.1%)
Adverse Event		
Neutropenia (ANC <1000/mm^3)	34 (44.2%)	352 (49.9%)
Anemia	5 (6.5%)	137 (19.4%)
Nausea	14 (18.2%)	119 (16.9%)
Asthenia	5 (6.5%)	70 (9.9%)
Hypochromic Anemia	4 (5.2%)	69 (9.8%)
Thrombocytopenia	5 (6.5%)	65 (9.2%)
Fever	6 (7.8%)	64 (9.1%)
Alopecia	7 (9.1%)	63 (8.9%)
Alkaline Phosphatase Increase	1 (1.3%)	55 (7.8%)
Vomiting	6 (7.8%)	55 (7.8%)
Diarrhea	4 (5.2%)	55 (7.8%)
Stomatitis	4 (5.2%)	48 (6.8%)
Oral Moniliasis	1 (1.3%)	39 (5.5%)

The following additional (not in table) adverse events were observed in AIDS-KS patients; only events considered at least possibly drug-related by investigators are included.

Incidence 1% to 5%

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

Cardiovascular: chest pain, hypotension, tachycardia.

Cutaneous: Herpes simplex, rash, itching.

Digestive System: mouth ulceration, glossitis, constipation, aphthous stomatitis, anorexia, dysphagia, abdominal pain.

Hematologic: hemolysis, increased prothrombin time.

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

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

Incidence Less Than 1%

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

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

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

Endocrine System: diabetes mellitus.

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

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

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

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

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

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

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

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

glycosuria, kidney failure.

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

Ovarian Cancer Patients

Doxil® (doxorubicin HCl liposome injection) should be administered intravenously at a dose of 50 mg/m^2 (doxorubicin HCl equivalent) at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related AEs are observed, the rate of infusion can be increased to complete administration of the drug over one hour. The patient should be dosed once every 4 weeks, for as long as the patient does not progress, shows no evidence of cardiotoxicity (see **WARNINGS**), and continues to tolerate treatment. A minimum of 4 courses is recommended because median time to response in clinical trials was 4 months. To manage adverse events such as PPE, stomatitis or hematologic toxicity the doses may be delayed or reduced (see Dose Modification guidelines below). Pretreatment with or concomitant use of antiemetics should be considered.

AIDS-KS Patients

Doxil® (doxorubicin HCl liposome injection) should be administered intravenously at a dose of 20 mg/m^2 (doxorubicin HCl equivalent) over 30 minutes, once every three weeks, for as long as patients respond satisfactorily and tolerate treatment.

General

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

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

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

Doxil® should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of Doxil®, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. **Doxil® must not be given by the intramuscular or subcutaneous route**.

Dose Modification Guidelines

Doxil® exhibits nonlinear pharmacokinetics at 50 mg/m^2; therefore, dose adjustments may result in a non-proportional greater change in plasma concentration and exposure to the drug. (see **CLINICAL PHARMACOLOGY, Pharmacokinetics.**)

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

Recommended Dose Modification Guidelines

PALMAR - PLANTAR ERYTHRODYSESTHESIA	
Toxicity Grade	**Dose Adjustment**

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

HEMATOLOGICAL TOXICITY			
GRADE	**ANC**	**PLATELETS**	**MODIFICATION**
1	1500 – 1900	75,000 - 150,000	Resume treatment with no dose reduction
2	1000 - <1500	50,000 - <75,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction
3	500 – 999	25,000 - <50,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction

4	<500	<25,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose at 25% dose reduction or continue full dose with cytokine support.

STOMATITIS	
Toxicity Grade	**Dose Adjustment**
1 (painless ulcers, erythema, or mild soreness)	**Redose unless patient has experienced previous Grade 3 or 4 toxicity.** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2 (painful erythema, edema, or ulcers, but can eat)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, Doxil® should be discontinued.
3 (painful erythema, edema, or ulcers, but cannot eat)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, Doxil® should be discontinued.
4 (requires parenteral or enteral support)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, Doxil® should be discontinued.

Patients with Impaired Hepatic Function

Limited clinical experience exists in treating hepatically impaired patients with Doxil®. Based on experience with doxorubicin HCl, it is recommended that Doxil® dosage be reduced if the bilirubin is elevated as follows: Serum biliribin 1.2 to 3.0 mg/dL give ½ normal dose, >3 mg/dL give ¼ normal dose.

Preparation for Intravenous Administration

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

Do not use with in-line filters.

Do not mix with other drugs.
Do not use with any diluent other than 5% Dextrose Injection.
Do not use any bacteriostatic agent, such as benzyl alcohol.
Doxil® is not a clear solution but a translucent, red liposomal dispersion.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

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

Procedure for Proper Handling and Disposal
Caution should be exercised in the handling and preparation of Doxil®.

The use of gloves is required.

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

Doxil® should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of Doxil®, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. Doxil® must not be given by the intramuscular or subcutaneous route.

Doxil® should be handled and disposed of in a manner consistent with other

anticancer drugs. Several guidelines on this subject exist.[2-8]

HOW SUPPLIED

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

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

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

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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-718/S-006

MEDICAL REVIEW(S)

MEDICAL TEAM LEADER COMMENTS ON NDA

NDA# 50-718/ SE1-006
Drug: DOXIL® (doxorubicin HCL liposome injection)

This application is for accelerated approval of DOXIL for the following indication:

> "The treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory is defined as a patient having progressive disease while on treatment, or within 6 months of completing treatment."

Under accelerated approval regulations, for indications where the new drug appears to provide benefit over available therapies, accelerated approval may be granted on the basis of a surrogate endpoint that is reasonably likely to predict clinical benefit. After approval, the sponsor is required to perform a phase 4 study to demonstrate that treatment with the drug is indeed associated with clinical benefit.

For this application, the surrogate endpoint is objective response rate. The Agency determined that, from a regulatory standpoint, there is no available therapy for the proposed indication. The following are the reasons for this determination:

- No drug has been approved for the treatment of ovarian cancer refractory to platinum compounds and paclitaxel, and

- There is not a substantial body of other evidence demonstrating the efficacy of a drug for this indication.

This issue was discussed with the Oncologic Drugs Advisory Committee (ODAC). Although there have been reports of other drugs producing a similar response rate in refractory ovarian cancer, the trials were small and they have not been subjected to rigorous FDA scrutiny of claims of "refractoriness" and of response rate; furthermore, literature reports are subject to reporting bias. It is unlikely that a negative trial, such as study 30-47E, reported in the Doxil sNDA, would have been reported in the literature.

The central question posed to ODAC was whether the findings presented in the application are reasonably likely to predict clinical benefit. The FDA analyses of response rates from 3 phase 2 trials and the interim findings from a phase 3 trial are presented in the following table:

Summary of Clinical Studies from Which the Combined Overall Response Rate of DOXIL in the Platinum- and Paclitaxel-Refractory Population is Estimated

Study Number	Clinical Phase	No. Patients	Completion Status	Study Location	Response Rate in Refractory Dz.	Exact 95% CI
30-22*	II	35	Completed	2-center US	22.2% (6/27)	8.6% –42.3%
30-47**	II	89	Completed	Multi-center US	17.1% (14/82)	9.7 – 27.0%
30-47E**	II	52+	Ongoing	Multi-center Europe	0.0% (0/36)	0.0 – 9.7%
30-49**	III	237	Ongoing	Multi-center US + Europe	DOXIL 13.6% (6/44) vs. Hycamtin 8.1% (3/37)	5.2 – 27.4% 1.7 – 21.9%
Combined Data from Doxil Arms					**13.8% (26/189)**	**9.2% – 19.5%**

*Used every-3-week schedule of DOXIL.
** Used every-4-week schedule of DOXIL.

The sample size is impressive, but the response rate of 14% is low. To assist committee members in evaluating whether the data on objective response were "reasonably likely to be associated with clinical benefit," the reviewers provided the advisory committee members with a table (attached) that described the bulk of disease (number of lesions, disease sites, and baseline measured tumor area) and the quality of the response (minimum tumor area and duration of response). It is not clear whether committee members took these factors into consideration, as they were not discussed during the committee deliberations. The committee members were perplexed at the 0% response rate in the 36-patient European trial. None of the numerous prognostic factors evaluated by the sponsor adequately explained the lack of tumor response in this trial. Despite the low response rate, the committee felt that these responses were reasonably likely to be associated with clinical benefit, as they voted in the affirmative (9 to 2), to the following question:

> Do the data on objective response indicate that DOXIL is "reasonably likely" to be associated with clinical benefit in this population?

Both of the experts in gynecologic cancers (Drs. Ozols and Nerenstone) voted in the affirmative.

The committee was then presented with the following data on toxicity:

"More toxicity was noted with the every-3-week schedule than with the every-4-week schedule. Consequently, only the latter schedule is proposed for approval. Toxicity attributed to DOXIL in study 30-47, the largest study where DOXIL was given by the every-four-week schedule, is outlined in the following table from the application:

Event	% patients	severe
PPE**	42%	20%
Asthenia	42%	9%
Leukopenia	39%	7%*
Anemia	39%	14%
Nausea	38%	7%
Neutropenia	37%	16%*
Stomatitis	35%	9%*

* including Grade IV events
**PPE = Palmar-plantar-erythrodysesthesia"

The committee then voted in the affirmative (9 to 2) to the following question:

> "Considering the efficacy discussed in question #1 and the toxicity described above, do you recommend that DOXIL, 50 mg/M2 administered intravenously every 4 weeks, be granted accelerated approval for the treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regimens? (Refractory is defined as a patient having progressive disease while on treatment, or within 6 months of completing treatment.)"

The advisory committee is consulted for pivotal clinical judgements. The committee appeared to fully understand the FDA presentation of the data. Consequently, with a strong majority of the committee voting that the data in this application are reasonably likely to predict clinical benefit, I concur with the committee recommendation that DOXIL be granted accelerated approved for the treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regimens.

Grant Williams MD 6/24/99
Grant Williams, MD
Team Leader
Division of Oncology Drug Products

I concur with Dr. Williams' recommendation

Robert L. Justice, MD
6/25/99

Table of Baseline and Response Data in Responders, From Phase 2 Trials

Patient ID	Response	Number of Lesions	Disease Sites	Baseline Lesion Area	Best Response Lesion Area	Duration of Response (Weeks)
(b) (6)	PR	3(2)	liver, soft tissue-pelvis	7	0	61.0
	PR	7(6)	liver, pelvis, lymph nodes	48.86	11.84	39.4
	PR	2(1)	soft tissue-pelvis, lymph nodes	12.3	0	57.7
	PR	4(1)	liver, spleen, peritoneum, soft tissue-pelvis	6	0	67.0
	CR	3(2)	peritoneum, pelvic masses	106.13	1	65.1
	PR	3(1)	omentum, pelvic mass	36	4.84	19.0
	PR	2(2)	soft tissue	8.41	2.92	48.3
	PR	3(3)	lymph nodes	14.5	6.94	24.1
	PR	3(3)	liver, soft tissue	18.24	0	9.7
	PR	3(3)	lymph nodes, soft tissue	31	8.3	40.7
	PR	1(1)	pelvic mass	20	3.22	10.1
	PR	1(1)	peritoneum	9	0	26.3
	PR	1(1)	omentum	6.25	0.5	21.7
	PR	1(1)	splenic flexure modules	3.24	0	7.3
	PR	1(1)	vaginal mass, pelvic mass	4	1	16.1
	PR	5(5)	liver, abdominal mass	14.5	3	9.7
	PR	1(1)	liver	6.3	0	26.6
	PR	1(1)	soft tissue	9	1.43	20.3
	PR	6(6)	lymph nodes	76.64	10.5	23.1
	PR	1(1)	soft tissue mass	56	25	16.0
	PR	1(1)	pelvic mass	58.32	22.4	8.0

The notation a(b) in Number of Lesions means:

a – Number of Lesions Followed
b – Number of Lesions Measured

DRAFT

Medical Officer Review #1 of NDA Efficacy Supplement

1. General Information:
   1.1 NDA# 50-718; SE-006
   1.2 Drug Name
      1.2.1 Generic Name: doxorubicin HCl liposome injection
      1.2.2 Trade Name: DOXIL
   1.3 Sponsor/Applicant: ALZA Corporation
   1.4 Proposed Indication: paclitaxel- and platinum- refractory ovarian cancer (b) (4)
   1.5 Date submission received: 12/29/98
   1.6 Date of this review: 6/24/99
   1.7

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Introduction to and Regulatory History of sNDA 50-718

Last year, in a series of meetings, the applicant met with the agency to discuss the possibility of submitting an application for accelerated approval in patients with ovarian cancer refractory to platinum and paclitaxel. No drug is labeled for this indication. The debate during these meetings revolved around the meaning of the words "available therapy" in the accelerated approval regulations. The following is an excerpt from those regulations:

> CFR 314.500
>
> "This subpart applies to certain new drug and antibiotic products that have been studied for their safety and effectiveness in treating serious or life-threatening illness and that provide meaningful therapeutic benefit to patients over **existing** treatments (e.g., ability to treat patients unresponsive to, or intolerant of, **available** therapy, or improved patient response over **available** therapy)."

When there is no "available therapy," one may gain accelerated approval by demonstrating an advantage in a surrogate endpoint (e.g., response rate) that is "reasonably likely" to predict clinical benefit. The applicant must then perform a phase IV study after approval to verify that the drug indeed produces clinical benefit.

The Division of Oncology Drug Products recently evaluated what "available therapy" should mean in the context of accelerated approval of oncology drugs. Some would suggest that "available therapy" should be those drugs with that specific indication approved in labeling. This would encourage applicants to update their labels. It would also reflect the fact that findings, such as response rates, reported in the literature are often inflated relative to findings after full FDA review of the data. Others would argue that any drug reported in the literature with a reasonable response rate should be considered "available therapy," since off-label treatment of patients in oncology is a common practice. In consultation with a working group in the Center for Drugs Evaluation and Research, the division decided that "available therapy" would in most cases refer to drugs with labeled indications. In circumstances where there was very strong evidence of an effective unlabeled treatment in the literature, such a treatment might be considered as "available therapy." After these deliberations, the division informed the sponsor that an application for accelerated approval of doxil in paclitaxel- and platinum-refractory ovarian cancer could be submitted, with a projected response rate of 18%, in a database of about 100 patients.

As this review will demonstrate, the applicant and FDA are in near total agreement on the efficacy findings of this NDA. Combining patients from all phase II trials, the FDA finds a response rate of 13.8% (20/145) with 95% confidence intervals of 8-20%. This is similar to the applicant's finding of 14.4% (21/146) with 95% confidence intervals of 8.7-20.1%. Of the responses in question, one responder claimed by the applicant ((b) (6))

had nice tumor shrinkage, but did not appear to have the response confirmed prior to progression. The FDA reviewers note that several other patients might have been classified as responders had scans for verifying response status been done more frequently. In such cases, progression was documented at the delayed follow-up scan.

Overview of Studies Included in this Review

Study Number	Clinical Phase	No. Patients	Completion Status	Study Location	sNDA Location	Section in this Review
30-22	II	35	Completed	2-center US	V 6-9	8.1
30-47	II	89	Completed	Multi-center US	V 10-16	8.2
30-47E	II	52+	Ongoing	Multi-center Europe	V 18-21	8.3
30-49	III	176+	Ongoing	Multi-center US + Europe	V40-46	8.4
30-22IR		25	Completed	Baltimore, MD	V M52.1	8.5
30-47IR		59	Completed	Baltimore, MD	V 17	8.6

Summary of Clinical Studies from Which the Combined Overall Response Rate of DOXIL in the Platinum- and Paclitaxel-Refractory Population is Estimated

Study Number	Clinical Phase	No. Patients	Completion Status	Study Location	Response Rate	Exact 95% CI
30-22	II	35	Completed	2-center US	6/27 (22.2%)	8.6 – 42.3%
30-47	II	89	Completed	Multi-center US	14/82 (17.1%)	9.7 – 27.0%
30-47E	II	52+	Ongoing	Multi-center Europe	0/36 (0.0%)	0.0 – 9.7%
Combined		**176+**			**20/145 (13.8%)**	**8.1 – 19.8%**
30-49	III	176+	Ongoing	Multi-center US + Europe	DOXIL* 6/44(13.6%) vs. Hycamtin 3/37 (8.1%)	5.2 – 27.4% 1.7 – 21.9%

Independent Radiological Reviews of Studies 30-22 and 30-47

Study Number	Clinical Phase	No. Patients	Completion Status	Study Location	Response Rate	Exact 95% CI
30-22IR	--	25	Completed	Baltimore, MD	6/25 (24%)	9.4 – 45.1%
30-47IR	--	59	Completed	Baltimore, MD	8/59 (13.6%)	6.0 – 25.0%

8.1 Study 22

Pharmacokinetics and Response to DOXIL (STEALTH Liposomal Doxorubicin HCl) in Patients with Recurrent or Persistent Epithelial Ovarian Cancer After Initial Therapy with Platinum and Paclitaxel-based Regimens

8.1.1 Location of information reviewed in NDA:

Study Item	Volume
Study Report	6-9
Protocol	7
Listings	7 (p. 158)--9
CRF's	54-59
Database documentation	"dox30-22.mdb"
Integrated Summary of Efficacy	48

8.1.2 Important Study Dates

Study Period	September 1994 – July 1995
First Patient's First Treatment	30 Sep 94
Last Patient's First Treatment	14 Jul 95

8.1.3 Review of protocol and amendments

8.1.3.1 Protocol Amendments

Amendment #1 19 Oct 94 # Patients before amendment: 2

This amendment clarified a number of issues, some of which are of major significance to the conduct of the trial. Issues such as adding references, allowing investigator discretion about the use of CSF's, are considered minor. The next paragraph describes some changes that could have a significant impact on study conduct or results reporting.

Some of the changes which could have implications regarding study conduct or results reporting include: (1) changing the number of cycles required for completion of the protocol from 2 to 3 as well as increasing the number of cycles between disease status assessments (2) increasing the time between cycles to 28 days for PPED from 21 days and dose reducing 20% if delay is not sufficient; (3) clarifying the criteria defining "evaluable" disease; (4) clarifying a "durable" response as one that persists 4 weeks; (5) clarifying the criteria defining a "durable" "evaluable" response by CA-125 only

Amendment#2 16 Aug 95 (v6, p15/32)

Further changes of significance to the study conduct or results reporting include: (1) clarification of delay of additional cycles of DOXIL in the presence of PPE (see table below); (2) clarification about dose reduction for stomatitis, hematologic toxicity, and hyperbilirubinemia (see tables below); (3) further delineation of laboratory studies required for treatment beyond 10 cycles.

Guidelines for interval lengthening and/or dose reduction (v7, p54)

Palmar-Plantar Erythrodysesthesia

Grade 1	No previous grade 3-4	No change
	Previous grade 3-4	Delay next cycle 1 week
	Following a 2-week delay	Dose reduce 25% and cont. q 4 wk
Grade 2	No previous delay	Delay 1 week
	Following a 1-week delay	Delay 1 additional week
Following a 2-week delay		Dose reduce 25% and continue q 4 wk
Grade 3-4	No previous delay	Delay 1 week
	Following a 1-week delay	Delay 1 additional week
	Following 2 week delay	Discontinue therapy

Neutropenia or Thrombocytopenia

Grade 2-3	Delay until Grade 1
Grade 4	Delay until Grade 1 and either dose reduce 25% or use cytokine

Hyperbilirubinemia

1.2 mg/dL < Bili ≤ 3.0 mg/dL		dose reduce 25%
> 3.0 mg/dL	Unrelated to DOXIL	dose reduce 50%
	Related to DOXIL	discontinue DOXIL

Stomatitis

Same as dose modifications for PPED

Other Toxicities

Grade 3-4	Delay until Grade 1 + 25% reduce

8.1.3.2 Investigators

This was a 2-center US study. The following investigators are listed with their study site and accrual (v7, p159):

Muggia	Los Angeles, CA	22 patients
Hainsworth	Nashville, TN	13 patients

8.1.3.3 Objectives

There were 3 objectives to this study (v6, p15/32):

1. To determine the pharmacokinetics of DOXIL in patients with epithelial ovarian cancer
2. To define the response to DOXIL in patients with epithelial ovarian cancer who have failed treatment with both platinum-based and Taxol-based treatment regimens (v7, p8)
3. To evaluate the safety and tolerance of DOXIL

8.1.3.4 Rationale

Liposomal encapsulation of doxorubicin may overcome p-glycoprotein-mediated cellular resistance. In the phase I study of DOXIL in solid tumors, responses were noted in two patients suggesting potential activity of DOXIL in ovarian cancer. One patient with a peritoneal mesothelioma demonstrated a response, and one patient with ovarian cancer responded with a decrease in CA-125. In this phase I study two patients with multiply-refractory ovarian cancer and liver involvement demonstrated stable disease over 7 cycles of DOXIL at 40-60 mg/m2. Of the six other patients with ovarian cancer studied prior to initiation of this study, two experienced a decline in CA-125.

8.1.3.5 Inclusion/Exclusion Criteria

Histologically/cytologically proven ovarian cancer of epithelial origin

Recurrent or persistent ovarian cancer after initial therapy (platinum [cis or carbo] and paclitaxel) – did allow for intraperitoneal administration for which resistance or persistence must also be demonstrated

One of the following:

Bidimensionally measurable disease

Palpable disease with CA-125 > 100 U/mL

Unmeasurable CT abnormalities with CA-125 > 100 U/mL

Age ≥ 18 y/o

Labs: ANC ≥ 1,500/uL **AND** Plt > 100,000/uL **AND** Hgb ≥ 8g/dL **AND** Cr ≤ 2.0 mg/dL **AND** Bilirubin < 1.5 mg/dL

KPS ≥ 50%

Written informed consent

No prior anthracyclines

Pregnancy or breastfeeding patients excluded

Life expectancy < 3 mos excluded

Prior radiation to the mediastinum or pelvis excluded

Cardiac EF < 50% (by echo or isotopic methods) excluded

NYHA Class II or greater cardiac failure excluded

Infection: bacterial, viral , or fungal uncontrolled excluded

Patient non-compliance excluded

Prior treatment with investigational drug ≤ 30 days excluded (v7, p8)

Reviewer Comment: The time period within which recurrence would be considered "refractory" or "resistant" to platinum or paclitaxel was assumed to be six months, in similar fashion to study 30-47. This was clarified in a subsequent e-mail with sponsor.

8.1.3.6 Formulation

DOXIL is provided as a sterile, translucent, red liposomal dispersion in 10-mL glass, single-use vials, containing 20 mg of active drug. (v2, p2,6)

8.1.3.7 Experimental Controls

This is a single-arm 2-center domestic US study with no pre-specified stratification. There is no control arm.

8.1.3.8 Dosage Schedule

DOXIL 50 mg/m2 intravenously every three weeks. (v6, p3/20). The initial infusion was given at 1 mg/min to minimize the risk of infusion-related adverse effects. Subsequent infusions were given over 60 min if there was not initial infusion-related adverse events.

This study follows a 2-stage design. If one or more responses were observed in the first 14 patients, an additional 16 patients would be added to more accurately determine the response rate.

Reviewer comment: There is no discussion about the power to detect a given response rate, and what the type I error (alpha) assumption is.

Therapy was to be provided for three cycles. If progressive disease or significant adverse events (SAE) (not resolvable by treatment delay) were observed, the patient was removed from the study. If stable disease or partial remission was observed, the patient could remain on therapy until either (a) SAE was encountered, or 550 mg/m2 cumulative dose of DOXIL had been reached. If 550 was reached, and further continuation was deemed of interest by the investigator, repeat assessment of LVEF was necessary, and after each 180mg/m2 additional cumulative DOXIL administration. (v6, p3/20)

8.1.3.9 Follow-up Details

Refer to the Applicant's follow-up schema below. Patients meeting response criteria for a PR or CR were rescanned 2 months after the final cycle of DOXIL.

Activity	Pre-Treatment	During Treatment			After Treatment	Follow-up
	≤ 14 days pre-Study	Weekly After Each Dose	48 Hours prior to Cycle 2	End of Cycle 3 & Every 3 Subsequent Cycles	End of Treatment (3-4 weeks after last dose)	2 mos after end of final cycle (pts with PR or CR)
Informed Consent	X					
Medical History	X					
PE, Ht, Wt, KPS	X		X		X	
12-lead ECG	X				X	
Cardiac Ejection Fraction	X				X	X
CXR	X			X	X	X
CT or MRI	X			X	X	X
Lesion Measurement	X			X	X	
Blood Chemistry	X		X		X	
CBC w/ diff & plts	X	X	X		X	
CA-125	X		X		X	X
Plasma Samples	X				X	
Ascitic or Pleural Fluid	X				X	
Urinalysis	X				X	
Adverse Experiences		X	X		X	X
Evaluation of Response			X		X	X
Concomitant Medication	X		X		X	

8.1.3.10 Removal From Study

Patients' therapy was discontinued under any one or more of the following circumstances:

Disease progression
Clinical deterioration
SAE or intolerable AE
Grade 4 non-hem tox except stomatitis, PPDE, hyperbilirubinemia
Patient's request
Need for other drugs not allowed in the protocol

8.1.3.11 Efficacy Considerations

The primary efficacy endpoint was to be based on the proportion of patients with a durable response to therapy. A durable (confirmed) response was defined as a CR or PR that lasted at least 21 days.

Secondary endpoints included time to response, duration of response, and time to progression.

Each lesion evident on scanning was numbered and tracked. Lesions were either **measurable** or **evaluable**. Measurable lesions were bidimensionally measurable with clearly defined margin on CXR, scan, or physical examination. Evaluable lesions did not have clearly defined margins, and one dimension must have been at least 2 cm with both diameters ≤ 0.5 cm and CA-125 ≥ 100. (v6, p10)

8.1.3.11.1 Response Criteria

Complete Remission

Complete disappearance of all measurable and evaluable disease
AND
Resolution of ascites and effusions
AND
Normalization of CA-125 and all other labs evidencing tumor involvement
AND
No new lesions

Partial Remission

For measurable disease, 50% or greater decrease in sum of products of bidimensional perpendicularly measured lesions (instead of complete resolution) o/w identical to CR

For evaluable disease, the CA-125 which must be initially > 100, **and** must fall by 50% or more from the pretreatment level **and** complete resolution of at least 1 evaluable lesion, all of which must persist for at least 3 weeks.

Reviewer comment: FDA counted responses in the platinum- and taxane-refractory population from only patients with measurable disease, not evaluable disease.

Stable Disease

Change in measurable disease too small to meet PR criteria with no new lesions

Progressive Disease or Relapse

Increase in size of lesions > 25%
OR
Reappearance of new lesions which had disappeared

OR
Clear worsening of any evaluable disease
OR
Any new area of disease
OR
Progression on CA-125 alone
OR
Physiological evidence of progression: ascites, jaundice, pleural effusions, neuro changes. (v6, p11)

Time to Response: from first day of dosing to the first observation of a confirmed response

Duration of Response: from first observation of response till first observation of relapse

Time to Progression: from first day of study dosing to first observation of progressive disease or death, whichever is first. (v6, p12/29)

8.1.3.12 Safety Considerations

Adverse events were graded by the NCI-CTC. In addition, data regarding the use of G-CSF and cardiac ejection fraction data were collected.

8.1.4 Analysis of Study 30-22

8.1.4.1 Details of trial conduct and analysis

This was a 2-center US domestic study with 35 patients enrolled. The data submitted to the FDA are derived from patients who were accrued between 30 September 1994 and 14 July 1995.Twenty-two patients were enrolled in Los Angeles, CA and 13 were enrolled in Nashville, TN. (v6,p33)

The sponsor states that the study was in compliance with Good Clinical Practices, performed under IND (b)(4) under the approval of the relevant Institutional Review Boards, under local regulations Federal law, 21 CFR 56. Written informed consent was obtained from patients and the study followed ethical principles of the Declaration of Helsinki. (v6,p16)

Investigators and Distribution of 35 Enrolled Patients by Trial Center (v6,p33)

Investigator	Location	No. (%) of Patients
Hainsworth	Nashville, TN	13 (37.1%)
Muggia	Los Angeles, CA	22 (62.9%)

8.1.4.2 Baseline Patient Characteristics

Thirty-five patients were enrolled all of whom received treatment. Baseline demographics confirm that all patients were female, median age 65 (range 46-78) and ethnic distribution was 88.6% Caucasian, 2.9% Black, and 8.6% Asian.

The study population's median Karnofsky Performance Status was 80% (range 60-90%). Mean baseline cardiac ejection fraction was 67.2% (range 55-74%) for 35 patients.

Distribution by Stage at Diagnosis using ITT Population (ACCESS table "dxhist")

FIGO Stage	No. (%) of Patients
I	1 (2.9)
II	3 (8.6)
III	21 (60.0)
IV	10 (28.6)
Total	35 (100.1)

Distribution by Grade at Diagnosis using ITT Population (tables "histdat" + "dxhist")

Histologic Grade	No. (%) of Patients
Well Differentiated	1 (2.9)
Moderately Differentiated	3 (8.6)
Poorly Differentiated	15 (42.9)
Grade Not Specified	16 (45.7)
Total	35 (100.1)

Reviewer comment: Since this is a small single-arm uncontrolled trial, only limited conclusions may be drawn from the above information.

8.1.4.2.1 Prior Therapy

Prior therapy for cancer in the study population included chemotherapy and radiotherapy. Most of this section will focus on prior chemotherapy, but a few comments about prior radiotherapy might be in order.

Four of the 35 patients in the study population underwent radiotherapy prior to enrollment into study 30-22. Of the 4, 3 received therapy by linear accelerator technique and one received brachytherapy implants. One patient underwent radiotherapy with curative intent and achieved a CR. All other patients achieved only stable disease or progressive disease.

Independent FDA analysis of prior chemotherapy data in ACCESS table "chemo2" focused on date of last platinum and last taxane and date of recurrence. The criterion of recurrence or progression within six months of completing therapy or progression on therapy was used to determine "platinum- and taxane-" refractory status.

Twenty-six of the 35 patients enrolled in study 30-22 met the above criterion to be considered platinum- and taxane-refractory. The following table lists the patients and which agent failed to meet the criterion established above.

Patient ID	Last Platinum	Platinum Progression Date	Last Platinum-Progression	Last Taxane	Taxane Progression Date	Last Taxane-Progression
(b) (6)			**> 8 mos**	(b) (6)		> 4 mos
			~7 mos			~12 mos
			< 1 mo			**~8 mos**
			> 9 mos			< 1 mo
			zero			**> 9 mos**
			9 mos			< 1 mo
			8 mos			> 1 mo
			> 6 mos			> 2 mos
Total=8						

The sponsor defines a subpopulation of the ITT population which is termed "evaluable" and which received three cycles or more. This "evaluable" subpopulation was not defined prospectively in the protocol document. It is not to be confused with the other use the sponsor makes of the term "evaluable" which refers to disease status that does not meet "measurable" status but which still meets the eligibility criteria and is not visualized with distinct borders by the imaging modality chosen for the particular patient.

Reviewer comment: Clearly patients who receive only one to three cycles of therapy due to disease progression, disease-related AE's, or drug-related AE's would be expected, as a group to have a lower response rate than the whole eligible ITT population. Thus, a significant bias is introduced when a poorer-responding subpopulation is subtracted out

of the denominator thereby causing the calculated response rate to increase. For FDA analysis, the denominator included all those patients progressing on therapy or relapsing within six months following platinum- and taxane-based therapy. The numerator is derived from these same patients but who have measurable disease who met the criteria for response defined above.

8.1.4.3 Therapy Delivered

The ITT population of all 35 patients is used in the FDA analysis of therapy delivered, and drawn from ACCESS table "doseall" supplied electronically accompanying the sNDA submission.

The following table summarizes the delivered doses by patient number and in comparison to that, which would be expected with no dose reductions.

No. Cycles	No. Patients	Expected Cumulative Dose	Range of Cumulative DOXIL (mg/m2)
1	2	50	50-50.3
2	4	100	90-100
3	8	150	149.03-150.9
4	2	200	190-200
5	0	250	--
6	4	300	239-262.5
7	1	350	310
8	1	400	400
9	2	450	390-400.36
10	0	500	--
11	2	550	537.33-550
12	0	600	--
13	1	650	600
14	1	700	590
15-18	0	750-900	--
19	3	950	780-810
20	1	1000	830
21	1	1050	745.61
22	1	1100	840.32
23	0	1150	--
24	1	1200	1049.81
	Total = 35		

Independent analysis of all doses administered by the medical reviewer is derived from the ACCESS table "doseall".

There were a total of 292 intravenous administrations of DOXIL. Of this total 167 (57%) required a dose reduction. The reduced doses ranged from 44mg/m2-32mg/m2. The remaining 125/292 (43%) doses were given at the full dose of 50 mg/m2.

Analyzed in terms of delay, of the 292 administrations, 179/292 (61%) required delay or one week or greater, while 113/292 (39%) did not require any delay over 6 days.

The two analyses may be combined to consider combined dose reduction and delay. The table below indicates the number and percentage of all DOXIL administrations, which required reducing the dose, delaying the dose, or both.

No Reduction No Delay **82 (28.1)**	Reduction No Delay **31 (10.6%)**
No Reduction Delay **43 (14.7)**	Reduction Delay **136 (46.6%)**

Another way to analyze these data is to determine the likelihood that sufficient toxicity will be encountered such that dose reduction and/or delay becomes necessary. Of the 35 patients comprising the ITT population, 29 (82.8%) completed the protocol-specified 3 cycles. Of these 29 who completed at least three cycles, 27 required dose delay and 18 required dose reduction. Only 2 patients did not require either a dose reduction or delay, and 25/29 (86.2%) required both dose reduction and dose delay.

Reviewer comment: Thus, it is apparent that under the dose administration schedule specified by this protocol, that is 50mg/m2 every three weeks, AE's were common which requiring both dose reduction and delay.

8.1.4.3.1 Termination

Sponsor's tabular summary of terminations is excerpted below (v6,p43/60).

Sponsor's Summary of Termination

Complete Protocol	1 (2.9)
Continuing Treatment	0 (0.0)
Adverse Event/Toxicity	7 (20.0)
Disease Progression	27 (77.1)
	Total = 35

FDA Analysis of Reasons for Termination

Continuing on study	0 (0.0)
Progressive Disease	28 (80.0)
Physician Discretion	0 (0.0)
Adverse Events	5 (14.3)
Death on Study	0 (0.0)
Unclear	2 (5.7)
Lost to Follow-up	0
	Total = 35 (100.0)

The small differences between Sponsor and FDA analysis arise from a detailed review of the following factors: **disease status** (measurable > evaluable), **CA-125**, and **adverse events** due to either drug administration or disease progression. In two cases, the factors underlying the decision to terminate are unclear to the FDA reviewer following review of electronic databases and CRF's. In general, however, the overwhelming majority of terminations from this study, 80% of the total, were due to disease progression, and no terminations were found to be due to death on study.

8.1.4.4 Patient Follow-up and Disposition

The protocol specified that patients were to be followed for 2 months after the final cycle with cardiac ejection fraction evaluation, CXR, tumor evaluation by CT or MRI, CA-125 and review of any adverse events.

8.1.4.5 Evaluation of Efficacy

8.1.4.5.1 Sponsor's Evaluation of Efficacy of Primary Endpoint

Sponsor's evaluation of efficacy with respect to the platinum- and taxane-refractory population is excerpted below (v6, p22/39):

"Response rates are presented in Tables 12 and 13 for the double-refractory subgroup. Six (24.0%) of the 25 evaluable double-refractory patients responded to DOXIL therapy; 1 (4.0%) patient had a CR, and 5 (20.0%) had PRs. The 95% confidence interval (CI) for this response rate was 7% to 41%. Two (8%) double-refractory patients were unconfirmed responders; 8 (32%) doubles had SD, and 9 (36%) had PD at the time of study termination."

TABLE 12
SUMMARY OF ONSET AND DURATION OF INVESTIGATOR THERAPEUTIC REPSONSE
DOUBLE REFRACTORY PATIENTS FROM EVALUABLE POPULATION

	Doxil
Number of Patients	25
Responders:	6 (24.0%)
Complete Response	1 (4.0%)
Partial Response	5 (20.0%)
95% Confidence Interval for Responder Rate	(7%, 41%)
Non Responders:	
Unconfirmed Partial Response	2 (8.0%)
Stable Disease	8 (32.0%)
Progressive Disease	9 (36.0%)
For Responders Only:	
Time to Response (Days)	
N	6
Median	151.0
Range	88 to 203
Duration of Response (Days)	
N	6
% Censored	16.7
Median	427.0
Range	133 to 469
For All Patients:	
Time to Progression (Days)	
N	25
% Censored	8.0
Median	172.0
Range	54 to 789+

TABLE 13
SUMMARY OF ONSET AND DURATION OF INVESTIGATOR THERAPEUTIC REPSONSE
DOUBLE REFRACTORY PATIENTS FROM INTENT TO TREAT POPULATION

	Doxil
Number of Patients	28
Responders:	6 (21.4%)
Complete Response	1 (3.6%)
Partial Response	5 (17.9%)
95% Confidence Interval for Responder Rate	(6%, 37%)
For Responders Only:	
Time to Response (Days)	
N	6
Median	151.0
Range	88 to 203
Duration of Response (Days)	
N	6
% Censored	16.7
Median	427.0
Range	133 to 469
For All Patients:	
Time to Progression (Days)	
N	28
% Censored	7.1
Median	160.0
Range	15 to 789+

Reviewer comment: The sponsor in the above tables uses a definition of "evaluable" for patients that received two or more doses of DOXIL. This is a *post hoc* definition and not specified in the protocol document. Its effect is to exclude from the ITT population a less responsive subpopulation, which thereby increases the apparent response rate.

Reviewer Comment: Sponsor claims a CR for patient (b) (6). Review of the electronic database and CRF indicates that this patient achieved a PR. While the response was excellent, that is disease of 105cm2 was reduced to 1cm2, with concomitant normalization of CA-125, the criterion of complete disappearance of measurable disease was not met.

8.1.4.5.2 Reviewer's Evaluation of Efficacy of Primary Endpoint

FDA medical officer's review centered on identifying the platinum- and taxane-refractory group within the ITT population as the denominator for the response rate calculation. The FDA review process started with the electronic database "aomdfile." Cross-sectional areas calculated from serial tumor measurements were compared to the baseline cross-sectional area. The protocol-specified criteria for response, stable disease, and progressive disease were applied. All 35 patients in the ITT population underwent this analysis. Their "refractory" status was determined separately.

Reviewer comment: The medical officer applied standard criteria for confirmation of tumor response. An unconfirmed response is not likely to be of value as a surrogate for clinical benefit.

FDA analysis reveals 6 responses (all PR) in the platinum- plus paclitaxel-refractory ITT population of 27 patients, resulting in a response rate of 6/27 or 22.2% (exact 95%CI 8.6 – 42.3%). The exact 95 % confidence interval was calculated under the assumption of a binomial distribution.

Secondary Endpoints in Responding Patients

Patient ID	R	Start of DOXIL therapy	Date of Response ("aodfile")	Date of Relapse ("aodfile")	Date of Death (CRF)	TTR	DOR	Surv
(b) (6)	PR				(b) (6)	178	418	611
	PR					87	270	728
	PR					198	275	594
	PR					163	502	665
	PR					149	447	
	PR					122	129	248
Total=6								

* Three dates are given ~8 mos apart, for cycle 13 scans. ALZA has been queried about date of death.

8.1.4.5.3 Evaluation of Efficacy -- Secondary Endpoints

Sponsor (v6, p22/39):
"For the double-refractory patients, the median time to response for those patients who responded to therapy was 151 days (21.6 weeks), with a range of 88 to 203 days (12.6 to 29.0 weeks); the median duration of response was 427 days (61 weeks), with a range of 133 to 469 days (19.0 to 67.0 weeks) (Table 12). The median time to progression for all evaluable double-refractory patients was 172 days (24.6 weeks) with a range of 54 to 789+ (7.7 to 112.7+ weeks)."

Reviewer comment: This is an uncontrolled trial and hence difficult to derive any meaningful conclusions from analysis of the secondary endpoints above, although the FDA has independently derived numbers for these endpoints.

8.1.4.5.4 Evaluation of CA-125 Values

Sponsor (v6, p23/40):
"The median CA-125 at baseline was 164.5 U/mL; mean was 1356.1 U/mL; range was 20 to 14012 U/mL. Table 14 summarizes the CA-125 levels by cycle. No trend is noted in CA-125 levels with increasing cycles; however, the data are confounded by the fact that progressing patients are removed from the study and not re-dosed. Figures 4 and 5 illustrate the general decrease in CA-125 levels for all patients during the course of the study. CA-125 levels for individual patients are provided in Listing 16 (Appendix 11.10)."

Reviewer comment: Sponsor claims that no trend is noted in CA-125 levels with increasing cycles. FDA reviewer did note some relationship with initial dosing of patents and decline in CA-125 in some patients, but the level of decline, its rate of decrease, and the number of cycles over which the CA-125 stayed lower is highly variable, and no mathematical or statistical analysis is intended.

8.1.4.6 Analysis of Safety

8.1.4.6.1 Deaths

Sponsor (v6,p25/42):
"Twenty-five (71.4%) of the 35 patients died; 8 patients died within 8 weeks after discontinuation of therapy with DOXIL. All deaths were due to disease progression (Table 15). None of the deaths were considered related to study drug. The median survival time for all patients was 376 days (53.7 weeks) from the time of study entry, with a range of 44 to 1213+ days (6.3 to 173.3+ weeks) (Figure 6)."

Reviewer comment: Medical officer review of electronic records and CRF's confirms that no deaths occurred on study. Further descriptive analysis by the sponsor was not replicated.

8.1.4.6.2 Serious Adverse Events

Sponsor (v6, p25-6/42-3):
"Fifteen (42.9%) patients had serious adverse experiences for which they were hospitalized. For 12 of these patients, the events were considered to be unrelated to study drug. Three patients experienced events that were considered by the investigator to be possibly or probably related to study drug, and two of the three patients were discontinued from the study due to these events; summaries of these events are provided below. Summaries for all 15 patients who experienced serious adverse events are provided in Appendix 11.7.

- Patient (b) (6): This 63-year-old white female with a history of ovarian cancer, status post paclitaxel, cisplatin, carboplatin and FUDR, was hospitalized for pulmonary edema and congestive heart failure 15 days following her 19th dose of DOXIL. Her cumulative DOXIL dose was 780 mg/m^2. The patient's baseline LVEF per MUGA was 65%. Subsequent MUGAs showed the LVEF to be 67%, 62% and 61% after the 5th, 15th and 18th cycle. The patient experienced weakness, shortness of breath, and cough. Her blood pressure was 197/104, and an examination revealed diffuse lung rales and bilateral lower extremity edema. Diagnostic tests indicated pulmonary edema, congestive heart failure, and worsening of renal insufficiency. The patient was treated with oxygen, Lasix, Prazosin, Nitropaste, Isosorbide, and Kayexalate. She improved and was discharged after 4 days in the hospital. The investigator indicated that the event was possibly related to the study drug, but the study notes reveal that it was more likely due to increasing renal insufficiency and systemic arterial hypertension. The patient was discontinued from the trial due to this adverse event.

- Patient (b) (6): This 66-year-old white female was hospitalized for rehydration and administration of blood products approximately 2 weeks after receiving her first dose of DOXIL. She experienced weakness, anemia, nausea and vomiting, diarrhea and thrombocytopenia. She received six units of random donor platelets and one unit of packed red blood cells. The event was assessed as probably drug related. This patient continued on study and received two more cycles before being discontinued for progressive disease.

- Patient (b) (6): This 66-year-old white female was hospitalized for sepsis after 6 cycles of DOXIL. After a 4-day history of worsening cough, fever, chills, and head congestion, the patient was admitted for evaluation of sepsis. The patient had a fever (102°F) and the following lab values: WBC 12.7, hemoglobin 8.3. The patient was treated with IV Zosyn and pain medication for a sore throat and discharged from the hospital after 3 days. The sepsis was considered possibly related to study drug. Six days following her discharge from the hospital, the patient was readmitted for fever of unknown origin and cough. The investigator indicated that the event was severe and possibly related to the study drug. She continued on study to receive a total of 22 cycles of DOXIL.

This patient was hospitalized again for treatment of increasing respiratory symptoms 12 days following her 22nd dose of DOXIL. She had a history of systemic arterial hypertension and atypical chest pain, and her baseline MUGA showed a LVEF of 55%. Follow-up MUGAs were 67%, 65% and 75% after cycles 5, 8 and 17. An echocardiogram LVEF performed after cycle 19 was 45%, with evidence of increased blood pressure and tricuspid regurgitation. She had a 6-day history of cough, dyspnea and shortness of breath. She treated herself at home with albuterol inhaler without resolution of her symptoms. A chest x-ray showed increased interstitial fluid and infiltrates in bilateral bases with bilateral pleural effusions. She was treated with Zosyn and Proventil inhaler. She improved and was discharged from the hospital after 2 days on Floxin, Proventil, Lasix and potassium treatment. This was deemed probably related to DOXIL. The patient was removed from the study because of congestive heart failure and pulmonary edema. Fifty-one days following her 22nd dose she was admitted for shortness of breath and treated with oxygen, Lanoxin, Vasotec and diuretics. This also was deemed to be probably related."

Reviewer comment: In this study, there were only three grades of toxicity: 1-3. The reviewing medical officer's definition of an SAE was either grade 3 hematologic toxicity or grade 3 non-hematologic toxicity.

Reviewer comment: Review of the AE's included review of all AE's for each patient from the electronic database "aemax". This was supplemented by review of the CRF's felt necessary to further understand the clinical condition, concomitant medications, etc. In general, there was good concordance between the table "aemax" and the source of the information for this table, namely the CRF's.

Reviewer comment: Each patient's case was reviewed for the spectrum of toxicity and the maximum grade of each AE. This was combined with data about dose delay and dose reduction in an effort to review adherence to protocol and to better understand the management of each patient.

Reviewer comment: Hospitalizations were not always well-documented in the CRF's. Even so, the CRF's of the three patients briefly described, essentially confirms sponsor's summaries. One item of concern stemming from patient (b) (6) was the large discordance between the LVEF determined by two methods: MUGA and echocardiogram. LVEF by MUGA after cycle 17 was 75% (per CRF), but LVEF by echocardiography after cycle 19 was 45%. MUGA is generally regarded as more reproducible for LVEF than echocardiography, and the patient had had serial LVEF's by MUGA, all of which were quite close in value. This example suggests that the echocardiographically determined LVEF may not represent the true LVEF.

8.1.4.6.3 FDA Overall Analysis of SAE's

Taking the 35 patient ITT population and analyzing ACCESS table "aemax" the following observations were made. Of the 35 patients enrolled, 33/35 (94.3%) experienced a grade 3 (the maximum on this trial's toxicity scale) AE. Of those 33 patients experiencing at least one grade 3 AE, 23/33 (69.7%) had at least one AE that was judged either PROBABLY or POSSIBLY related to DOXIL. The two patients that did not experience grade 3 AE each received 3 cycles of DOXIL, and did require dosing delay though no dose reduction.

Sponsor analysis of discontinuation from study due to adverse events (v6,p26/43):

"Seven (20.0%) patients withdrew from the study due to severe adverse events (Table 6). Five of the 7 patients discontinued due to adverse events that were considered unrelated to study drug; these unrelated events included asthenia and peripheral edema (Patient (b)(6)), intestinal fistula and deep thrombophlebitis (Patient (b)(6)), pulmonary edema (Patient (b)(6)), bronchitis and/or possible pneumonia (Patient (b)(6)), and ascites (Patient (b)(6)). Although the patient listing for adverse events (Listing 14) and for termination reasons (Listing 7) listed Patient (b)(6) as withdrawing from the study due to an adverse event, the investigator considered ascites a sign of progressive disease and made the following note on the termination form for this patient: "unsatisfactory therapeutic response or disease progression.

Two patients withdrew due to events considered possibly related to study drug: Patient (b)(6) withdrew due to severe stomatitis, and Patient (b)(6) experienced dehiscence of a repaired hernia. Reasons for termination are provided for individual patients in Listing 7 (Appendix 11.10).

A third patient (Patient (b)(6)) was also listed as withdrawing from the study due to DOXIL-related adverse events as described in Section 7.1.2. This patient was reported as completing the study with a complete response during cycle 13. In violation of the protocol, the patient continued on study for a total of 22 cycles. Therefore, the adverse events that caused patient to discontinue treatment occurred after the patient completed the protocol. Because of this occurrence, there are discrepancies on the termination summary (Table 6), additional adverse events in Listing 14 and a discrepancy in the outcome of adverse events. The summary of adverse events that follows includes all of the events experienced by Patient (b)(6)."

Reviewer comment: Medical officer's review confirms the sponsor's summary.

8.1.4.6.4 Analysis of Organ-Specific AE's

8.1.4.6.4.1 Cutaneous Toxicity (PPE,HFS)

Characteristic of DOXIL is the associated cutaneous toxicity that manifests itself in protean forms, and is described by different terms including palmar-plantar erythrodysesthesia (PPE), hand-foot syndrome (HFS), vesiculobullous rash, exfoliative dermatitis, pruritis, rash, and skin discoloration.

Sponsor (v6, p29/46):
"Thirty (85.7%) patients experienced PPE that was probably or possibly related to treatment, making PPE the most frequently reported event with a possible relationship to DOXIL.

"Dosing every 3 weeks resulted in severe PPE in 10 patients, with the maximum occurrence after the third dose. After a median of 3 doses, (range 1-9 doses), all patients who continued to receive 50 mg/m^2/dose eventually required dose reductions and dose delay of at least 1 week because of skin toxicities. Two patients required further dose reductions from 40 mg/m^2 to 32 mg/m^2 due to stomatitis and/or skin toxicity. Skin rashes occasionally extended beyond palmar and plantar areas, such as over the shins (in sun damaged areas) or along intertriginous folds. Sixteen patients (45.7%) experienced rash; for 2 (5.7%) patients the event was severe in nature. Vesiculobullous rash was documented in 4 (11.4%) patients. Skin discoloration was reported in 11 (31.4%) patients. Increased pigmentation, including nail discoloration, was documented in four patients. Exfoliative dermatitis was documented in 7 (20.0%) patients; for 2 (5.7%) patients the event was severe."

Reviewer comment: Sponsor's findings are essentially confirmed. FDA analysis of cutaneous toxicity is inclusive of all toxicities named with the above terms. Of the 837 AE's included in the electronic table "aemax" 127/837 (15.2%) are related to the cutaneous toxicity associated with DOXIL use.

8.1.4.6.4.2 Mucositis

Mucositis is a toxicity occasionally encountered with DOXIL administration, and which can be seen in several forms. Other COSTART terms, which also are used, include: mucositis, mouth ulceration, stomatitis, esophagitis, dysphagia, mucous membrane disorder, and vulvar inflammation.

Sponsor (v6, p29/46):
"Four (11.4%) patients experienced mucous membrane disorder; all events were considered related to study drug. Three patients experienced prominent vulvar inflammation, and in two of these individuals, this was accompanied by a slowly resolving ulcerative lesion of less than 1 cm in diameter. 20 (57.1%) patients experienced stomatitis. All events were considered related to study drug, and for 6 (17.1%) patients the event was considered severe."

Reviewer comment: Medical officer review of table "aemax" essentially confirms the sponsor's findings described above.

8.1.4.6.4.3 Hematologic Toxicity

Myelosuppression has been noted with DOXIL, with all three hematopoietic lineages manifesting reduction in counts.

8.1.4.6.4.3.1 Anemia

Sponsor (v6, p31/48):
"Anemia was reported in 13 (37.1 %) patients; it was mild in 3 (8.6%), moderate in 7 (20.0%), and severe in 3 (8.6%) patients. Anemia was considered by investigators to be probably or possibly related to treatment in 12 (34.3%) patients. Five patients ((b) (6), (b) (6), (b) (6), (b) (6), (b) (6)) received epoetin alfa during the trial. Four of these patients had associated moderately severe anemia: (b) (6), (b) (6), (b) (6), (b) (6) (during cycles 1,17, 18 and 21, respectively). Patient (b) (6) received epoetin alfa in the first cycle at the discretion of the investigator."

Reviewer comment: Sponsor's findings are essentially confirmed. FDA review of table "aemax" under the COSTART term "anemia" revealed that 27 occurrences of anemia were noted, out a total of approximately 130 or 20% of all cytopenias reported. Of these 27, four (14.8%) were grade 3, 13 (48.1%) were grade 2, and 10 (37.0%) were grade 1. Treatment modalities included transfusions and epoetin alfa. Ten patients out of the 35 ITT population received a total of 33U packed red blood cells. One patient received epoetin alfa.

8.1.4.6.4.3.2 Thrombocytopenia

Sponsor (v6,p32/49):
"Thrombocytopenia was reported in 4 (11.4%) patients; it was mild in 2 (5.7%), moderate in 1 (2.9%), and severe in 1 (2.9%). The occurrence of thrombocytopenia was considered by the investigators to be related to treatment in all 4 patients."

Reviewer comment: FDA analysis of electronic table "aemax" found 4 reports of thrombocytopenia, of which one was grade 3, one was grade 2, and two were grade 1. One patient required a six-unit platelet transfusion. This essentially confirms the sponsor's claims.

8.1.4.6.4.3.3 Leukopenia/Neutropenia

Sponsor's analysis of leukopenia (v6,p31/48):
"Leukopenia was reported as an adverse event in 18 (51.4%) patients; in all 18 patients the event was considered possibly or probably related to DOXIL treatment. Leukopenia was mild in 5 (14.3%) patients, moderate in 7 (20.0%), and severe in 6 (17.1%)."

Sponsor's analysis of neutropenia (v6, p31/48):
"Neutropenia was reported in 18 (51.4%) patients; all events were considered possibly or probably related to study drug. The event was mild in 5 (14.3%) patients, moderate in 4 (11.4%), and severe in 9 (25.7%). Two patients (67034, 98031) had received G-CSF during the trial, both of which experienced severe, related neutropenia in the first cycle.

"Two patients had fever associated with neutropenia; both were considered serious adverse events by the investigator. Patient (b)(6) was admitted with neutropenia and fever 16 days after her first dose of DOXIL. Blood cultures were yeast positive; the most likely source appeared to be the PortaCath. She was treated with Neupogen and antibiotics, and she was removed from the study 2 days later because of progressive disease. The investigator did not think this event was related to DOXIL use. Patient (b)(6) was admitted with fever and neutropenia after her first cycle of DOXIL. The investigator thought this was not related to DOXIL, but to the intraperitoneal FUDR the patient received prior to entering the study."

Reviewer comment: Sponsor's findings are essentially confirmed. Medical review of table "aemax" revealed 105 cases of leukopenia out of 837 total adverse events. Of the 105 occurrences of leukopenia, 11/105 (10.5%) were grade 3, 42/105 (40%) were grade 2, and 52/105 (49.5%) were grade 1.

Reviewer comment: Closely related to leukopenia is neutropenia. Neutropenia is perhaps more significant in that it carries the risk of fever and infection, and these are directly related to the depth of the neutrophil nadir. Of the 837 AE's reported, 101/837 (12.1%) were neutropenia. Twenty-two of the 101 cases of neutropenia (21.8%) were grade 3, and it is these that represent the greatest risk of neutropenic fever, infection, or sepsis. Grade 2 neutropenia comprised 38/101 (38.6%) and grade 1 comprised 41/101 (40.6%) of all reported cases of neutropenia.

Sequelae of neutropenia were found in a number of patients in which both neutropenia and a fever or infection were associated in the same cycle of DOXIL therapy. The included two cases of oral moniliasis ((b)(6), and (b)(6)), furunculosis ((b)(6) and (b)(6)), sepsis ((b)(6)), gingivitis ((b)(6)) and neutropenic fever ((b)(6), (b)(6), (b)(6), (b)(6), and (b)(6)). Thus, fevers and/or a number of infectious diseases complicate neutropenia, which occurs with DOXIL therapy.

In summary, DOXIL's myelosuppressive capacity is well demonstrated, with decrease in all three hematopoietic lines, occasionally resulting in neutropenia with febrile and infectious complications, and the need for red cell and platelet transfusions.

8.1.4.6.4.4 Asthenia

Sponsor identifies this AE very briefly in the table below.

Reviewer comment: Review of asthenia in the table "aemax" revealed 24 of 35 (68.6%) patients experiencing one or more episodes of this AE. Eight patients (8/35 or 22.9%) were recorded to have had grade 3 asthenia, 10/35 (28.5%) experienced grade 2 asthenia, and 6/35 (17.1%) experienced grade 1 asthenia. This makes asthenia the second-most commonly encountered adverse event.

8.1.4.6.4.5 Gastrointestinal Adverse Events

Sponsor (v6,p32/49):

"Nineteen (54.3%) patients experienced nausea. For 13 (37.1%) patients, the nausea was considered possibly or probably related to study drug; for 3 (8.6%) of these patients, the nausea was severe. 17 (48.6%) patients experienced vomiting. For 9 (25.7%) patients, the vomiting was considered possibly or probably related to study drug; for 2 (5.7%) patients, the vomiting was severe. Antiemetic use had different patterns at each of the sites. At one site, 12 of 13 patients received antiemetics, 10 of whom received 5-HT_3 antagonists. At the other site, only 6 of 22 patients received antiemetics, only 1 received a 5-HT_3 antagonist. There was a difference in incidence of nausea and vomiting at the two sites, with the site which used more antiemetics recording a proportionate higher incidence. At the site which enrolled 22 patients, 12 patients had 28 adverse events involving nausea and vomiting (nausea: 7 grade I, 4 grade II and 2 grade III; vomiting: 8 grade I, 3 grade 2 and 4 grade III). At the site which enrolled 13 patients, 12 patients had 27 adverse events involving nausea and vomiting (nausea: 10 grade I, 1 grade II and 3 grade III; vomiting: 9 grade I, 2 grade 2 and 2 grade III).

"12 (34.3%) patients experienced diarrhea. For 6 (17.1%) patients, the diarrhea was considered possibly or probably related to study drug; it was not severe in any patient. Seven (20.0%) patients developed mild alopecia. For all seven of these patients, the alopecia was considered possibly or probably related to study drug."

Reviewer comment: FDA analysis of gastrointestinal adverse events included estimation of proportion of cases of nausea/vomiting, diarrhea, and gastritis.

A review of the sponsor's summary of antiemetic use and its potential use in mitigating against this adverse event suggests that the problem is not completely prevented with standard antiemetics, including the 5-HT3 antagonists. Vomiting was recorded 30 times in the table "aemax" of which 5/30 (16.7%) occurrences were grade 3, 8/30 (27%) were grade 2, and 17/30 (57%) were grade 1.

Seventeen cases of diarrhea were recorded in "aemax". Two were grade 3, six were grade 2 and 9 were grade 1. Attribution to DOXIL was divided evenly.

Lastly, 15 cases of gastritis were noted – all either grade 1 or 2 -- with attribution divided about DOXIL's role.

8.1.4.6.4.6 Serum Chemistry

Sponsor (v6, p33/50):

"A summary of maximum alkaline phosphatase, SGOT (AST), total bilirubin and serum creatinine values is found in Table 22. Maximum alkaline phosphatase and SGOT values remained near normal; mean maximum alkaline phosphatase and SGOT were 177.6 IU/L (range, 20 to 691) and 37.0 IU/L (range of 13 to 85), respectively. As shown in Table 23, both alkaline phosphatase and SGOT fluctuated minimally over the course of study. Figures 14 and 15 show baseline versus end-of-treatment plots for these values. Total bilirubin and serum creatinine fluctuated minimally over the course of the study (Table 24). Mean maximum total bilirubin and serum creatinine were 0.69 mg/dL (range, 0.3 to 1.3) and 1.26 mg/dL (range of 0.6 to 3.7), respectively. Baseline versus end-of-treatment scatter plots for these values are presented in Figures 16 and 17. No trends developed to suggest that DOXIL administration effected hepatic or renal parameters."

Reviewer comment: Medical officer visual inspection of most patients' values on a cycle by cycle basis revealed no significant trends or striking findings, with the exception of anecdotal moderate abnormalities. No end-organ related serum chemistry parameters appeared to be associated with cumulative DOXIL.

8.1.4.7 Safety Summary

Sponsor's summary table of adverse events (v6, p28/45):

Adverse Events Profile
(Reported in ≥10% of Patients)
(N = 35)

Adverse Event	No. of Patients Experiencing Event	
	All Events Reported	Probably or Possibly Related Events
PPE	30 (85.7%)	30 (85.7%)
asthenia	24 (68.6%)	21 (60.0%)
stomatitis	20 (57.1%)	20 (57.1%)
nausea	19 (54.3%)	13 (37.1%)
leukopenia	18 (51.4%)	18 (51.4%)
neutropenia	18 (51.4%)	18 (51.4%)
vomiting	17 (48.6%)	9 (25.7%)
rash	16 (45.7%)	15 (42.9%)
anemia	13 (37.1%)	12 (34.3%)
diarrhea	12 (34.3%)	6 (17.1%)
abdominal pain	11 (31.4%)	2 (5.7%)
skin discoloration	11 (31.4%)	11 (31.4%)
anorexia	11 (31.4%)	4 (11.4%)
gastritis	8 (22.9%)	8 (22.9%)
fever	7 (20.0%)	4 (11.4%)
constipation	7 (20.0%)	3 (8.6%)
alopecia	7 (20.0%)	7 (20.0%)
exfoliative dermatitis	7 (20.0%)	6 (17.1%)
peripheral edema	7 (20.0%)	2 (5.7%)
cough increased	7 (20.0%)	1 (2.9%)
intestinal obstruction	5 (14.3%)	0
dehydration	5 (14.3%)	3 (8.6%)
pharyngitis	5 (14.3%)	0
dyspnea	5 (14.3%)	2 (5.7%)
mucous membrane disorder	4 (11.4%)	4 (11.4%)
thrombocytopenia	4 (11.4%)	4 (11.4%)
vesiculobullous rash	4 (11.4%)	3 (8.6%)

Reviewer summary: The toxicity of DOXIL administered at 50 mg/m2 intravenously every three weeks was considerable, requiring dose delay, dose reduction, or both in the majority of administrations and patients. It appears to cause cutaneous toxicity in the form of hand-foot syndrome, and mucositis, manifesting itself as esophagitis and oral mucosal ulceration. In addition, there is frequent moderate and occasionally severe hematologic toxicity which, in this

study, resulted in infectious complications and transfusion requirements of both red cells and platelets. Other toxicities which were notable include nausea/vomiting and diarrhea.

Summary of Review of Study 30-22

DOXIL has been studied in the platinum- and taxane-refractory population. The primary efficacy endpoint was specified to be response rate. Thirty-five patients were enrolled. Five responses were confirmed in the double-refractory population of 26 patients, for a response rate of 19.2%, based on protocol-specified population, but 5/35 (14.3%) on an ITT basis. There were no CR's. There were no deaths attributable to DOXIL, although dose delay and/or dose reduction was common. Of the 35 enrolled patients 33 (94.3%), experienced a grade 3 toxicity, the highest number on this trial's toxicity grading scale. Approximately 70% of these 33 patients' adverse events were judged attributable to DOXIL. Adverse events commonly seen with DOXIL administration with this schedule included a 90% incidence of PPE, 70% incidence of asthenia, 60% incidence of stomatitis, myelosuppression consisting of anemia, leukopenia/neutropenia, and thrombocytopenia in 37%, 50%/50%, and 11% incidence respectively. Gastrointestinal adverse events including nausea/vomiting, anorexia, and gastritis generally attributable of DOXIL were noted with an incidence of 54%/49%, 31%, and23% respectively.

8.2 Study 47

A Noncomparative, Multicenter Study of DOXIL/CAELYX in the Treatment of Patients with Advanced Epithelial Ovarian Carcinoma

8.2.1 Location of information reviewed in NDA:

Study Item	Volume
Study Report	10-16
Protocol	11 (pp. 1-71)
Amendments	11 (pp. 72-94)
Listings	12-16
CRF's	54-59
Database documentation	"dox3047.mdb"
Integrated Summary of Efficacy	48

8.2.2 Important Study Dates

Study Period	July 1996 – June 1998
First Patient's First Treatment	25 Jul 1996
Last Patient's First Treatment	9 Dec 1997

8.2.3 Review of protocol and amendments

8.2.3.1 Protocol Amendments

Amendment #1 14 Jan 1997 (v11, p75-94) # pts accrued prior to amendment: 39

This amendment modified the study protocol in several ways. First, to clarify the study population, the definition of disease in this study was changed from "advanced" to "locally advanced or metastatic, refractory." Specifically, the population of platinum- and taxane-refractory patients is more precisely defined (v11, p81). Secondly, there was the addition of a health-related quality of life questionnaire. The purpose of this HQL was as a pilot only, and the data collected was not intended to be used in any claims. Thirdly, CA-125 was removed from the study protocol as an indicator of measurable disease, disease progression as it was determined that it was not a universally accepted marker of measurable disease or disease progression. Other minor changes including the duration of NED status acceptable prior to enrollment, frequency of laboratory studies, and recommendations for the use of cytokine therapy for the management of neutropenia.

Amendment #2 18 Nov 1997 (v11, p72-4)

This amendment modified the protocol to add topotecan resistance or refractoriness to the already platinum- and taxane-refractory population. Storage and administration specifications of DOXIL were also clarified.

8.2.3.2 Investigators

This is a multi-center US study involving 19 investigators. The six highest-accruing investigators are listed with their study site and accrual.

Gordon	Dallas, TX	26 patients
Granai	Providence, RI	10 patients
Rose	Cleveland, OH	9 patients
Hainsworth	Nashville, TN	6 patients
Lopez	Tucson, AZ	6 patients
Weissman	Albany, NY	6 patients(v12, p2)

8.2.3.3 Objectives

There are 3 objectives to this protocol

1. To describe objective response rates, time to response, duration of response, time to progression, and survival in patients with locally advanced or metastatic epithelial ovarian carcinoma who are refractory to platinum- and taxane-based chemotherapy and who have failed topotecan chemotherapy.
2. To assess the safety of DOXIL in this patient group
3. To obtain pilot data and information about the use of the HQL questionnaires for patients with ovarian cancer as well as monitor patients for changes during treatment when compared to baseline in measuring the effects of DOXIL on HQL in this clinical trial (US only)(v11, p13)

8.2.3.4 Rationale

Liposomal encapsulation of doxorubicin may overcome p-glycoprotein-mediated cellular resistance. In the phase I study of DOXIL in solid tumors, responses were noted in two patients suggesting potential activity of DOXIL in ovarian cancer. One patient with a peritoneal mesothelioma demonstrated a response, and one patient with ovarian cancer responded with a decrease in CA-125. In another phase I study two patients with multiply-refractory ovarian cancer and liver involvement demonstrated stable disease over 7 cycles of DOXIL at 40-60 mg/m2. Of the six other patients with ovarian cancer studied prior to initiation of this study, two have experienced a decline in CA-125. (v11, p12)

8.2.3.5 Inclusion/Exclusion Criteria

Histologically/cytologically proven ovarian cancer of epithelial origin (FIGO staging classification)

Measurable or Measurable and Evaluable disease, based on the following:

Measurable disease: bi-dimensionally measurable lesions with clearly defined margins by

Plain x-ray with at least one diameter greater than or equal to 0.5cm

OR

CT, MRI, or other imaging scan with both diameters > than the distance between cuts

OR

Palpation with both diameters greater than or equal to 2cm

Evaluable disease, having any one on the following:

Unidimensionally measurable lesions

OR

Masses with margins not clearly defined

OR

Lesions with both diameters less than or equal to 0.5cm

OR

Lesions on scan with either diameter smaller than the distance between cuts

OR

Palpable lesions with either diameter ≥ 2 cm

OR

Bone disease (v11 p28)

Two to three prior cytotoxic chemotherapy regimens allowed

Patients must be taxane and platinum refractory, based on the following:

Disease progression within 6 months of completing platinum- and taxane-based therapies

OR

Disease progression while receiving both platinum- and taxane-based regimens, either:

In combination

OR

Administered separately as single agents

OR

In combination with other drugs(v11, p15)

Patients considered topotecan refractory should have received prior platinum- and taxane-based regiments and topotecan

KPS ≥ 60%

Age ≥ 18 y/o

Labs: ANC ≥ 1,500/uL **AND** Plts > 100,000/uL **AND** Hgb ≥ 9g/dL

Labs: Cr ≤ 2.5 mg/dL

Labs: AST and ALT ≤ 2x ULN **AND** Alk phos ≤ 2x ULN **AND** Bilirubin ≤ ULN

LVEF ≥ 50% by MUGA

Written informed consent

Pregnancy or breastfeeding patients excluded

Life expectancy ≤ 3 mos excluded

Prior radiation to more than 1/3 hematopoietic sites excluded

NYHA Class II or greater cardiac failure excluded

Uncontrolled systemic infection

Prior treatment with investigational drug ≤ 30 days excluded

Prior therapy with DOXIL

Prior chemotherapy within 28 days for first dose of study drug (42 days for nitrosourea or mitomycin) (v11, p7-8)

Reviewer Comment: Patient non-compliance and prior anthracyclines were not stated as exclusion criteria. FDA interprets the above criteria as progression within 6 months of last platinum and progression within 6 months of last taxane.

8.2.3.6 Formulation

DOXIL is provided as a sterile, translucent, red liposomal dispersion in 20-mL glass, single-use vials.

8.2.3.7 Experimental Controls

This is a single-arm noncomparative multi-center domestic US study with no pre-specified stratification. There is no control arm.

8.2.3.8 Dosage Schedule

DOXIL 50 mg/m2 was administered intravenously every four weeks. (v11, p12). Normally infused over 1 hour, the first dose may be infused more to slowly mitigate against "occasional acute reaction" (v11,p44)

Therapy is given for six cycles, or until disease progression or dose-limiting toxicity. If the patient is still receiving clinical benefit after six cycles, further DOXIL may be administered.

Two-stage design: Accrue 33 then for 3 or fewer responses, the study is terminated. If 4 or more responses seen, 20 more patients are accrued. For 9 or more responses out of a total of 53 seen, there is a power of 85% that RR is at least 22% with alpha=0.0457 (v11, p32)

Guidelines for interval lengthening and/or dose reduction:

Palmar-Plantar Erythrodysesthesia

Grade 1	No previous grade 3-4	No change
	Pervious grade 3-4	Delay next cycle 1 week
	Following 2 week delay	Dose reduce 25% and cont. q 4 wk
Grade 2	No previous delay	Delay 1 week
	Following 1 week delay	Delay 1 additional week
	Following 2 week delay	Dose reduce 25% and cont q 4 wk
Grade 3-4	No previous delay	Delay 1 week
	Following 1 week delay	Delay 1 additional week
	Following 2 week delay	Discontinue therapy

Neutropenia or Thrombocytopenia

Grade 2-3	Delay until Grade 1
Grade 4	Delay until Grade 1 and either dose reduce 25% or use cytokine

Hyperbilirubinemia

• 1.2 mg/dL < Bili ≤ 3.0 mg/dL		dose reduce 25%
• > 3.0 mg/dL	Unrelated to DOXIL	dose reduce 50%
	Related to DOXIL	discontinue DOXIL therapy

Stomatitis

Same as dose modifications for PPED

Other Toxicities

Grade 3-4	Delay until Grade 1 + 25% reduce

8.2.3.9 Follow-up Details

Refer to the Applicant's follow-up schema below. Patients with meeting response criteria for a PR or CR were rescanned 2 months after the final cycle of DOXIL.

Activity	Pre-Treatment	During Treatment				After Treatment	Follow-up
	≤ 7 days pre-Study	Day 1	Weekly	Every Cycle	Every 8 Weeks (2 cycles)	End of Treatment (4 weeks after last dose)	2 mos after end of final cycle (pts with PR or CR)
Informed Consent	X						
Medical History	X						
Physical Examination	X			X	X	X	
QOL Questionnaire	X			X	X	X	
Radiological Assessment	X						
MUGA	X				X	X	
ECG	X						
Hematology	X		X	X	X	X	
Serum Chemistry	X			X	X	X	
Serum CA 125	X					X	
Serum pregnancy (test)	X	X					
Urinalysis	X				X	X	
DOXIL Administration		X					
Record Concomitant Meds		X	X		X	X	
Monitor Adverse Events		X	X		X	X	
Survival						X	

(v11, p8)

8.2.3.10 Removal From Study

Patients' therapy was discontinued under the following circumstances.

Disease progression
Clinical deterioration
SAE or intolerable AE which does not improve despite dose adjustment
Grade 4 non-hem tox except stomatitis, PPDE, hyperbilirubinemia
Patient's request
Need for other drugs not allowed in the protocol
Need for XRT

8.2.3.11 Efficacy Considerations

The primary endpoint is objective response rate as determined by physical examination and radiological assessments. (v11,p14)

CR is achieved when the following criteria are all met:

Complete disappearance of all measurable AND evaluable disease
No new lesions
No disease-related symptoms
Must persist for 4 weeks

PR is achieved when the following criteria are all met:

Did not achieve a CR
At least 50% decrease in the sum of the products of bidimensional perpendicular diameters of all measurable lesions
No progression of evaluable disease
No new lesions
Must persist for 4 weeks

Progressive Disease is achieved when any of the following are observed

50% or greater increase **or** increase **to** 10cm2 in the sum of the products of bidimensionally measured lesions over the smallest sum obtained at best response
Reappearance of any lesions which had disappeared
Clear worsening of any evaluable disease
Failure to return for evaluation due to death or deteriorating condition
Appearance of any new lesion/site(v11,p29)

Secondary endpoints include time to response, duration of response, time to progression, and overall survival.

Each lesion evident on scanning was numbered and tracked.

Time to Response: from first day of dosing to the first observation of a confirmed response

Duration of Response: from first observation of response till first observation of relapse

Time to Progression: from first day of study dosing to first observation of progressive disease or death, whichever is first. (v11, p29)

8.2.3.12 Safety Considerations

Adverse events were graded by the a company-unique toxicity scale (v11, p24)
Relationship to study drug was declared by the investigators as (probably- possibly-, or probably-not related)

8.2.4 Analysis of Study 47

8.2.4.1 Details of trial conduct and analysis

This was a multicenter US domestic study with 90 patients enrolled at 19 sites. The data submitted to FDA accrued between July 1996 and June 1998, although the study is still ongoing. Three sites accounted for half the patients in the study; 26 in Dallas, TX, 10 in Providence, RI, and 9 in Cleveland, OH. (v12,p2)

The sponsor states that ethical approval was obtained from appropriate IRB's and that written informed consent was obtained from each patient as required by 12 CFR 56.

Investigators and Distribution of Enrolled Patients by Trial Center (v11,p168 and v12,p2)

Investigator	Location	No. (%) of Patients
Del Prete	Stamford, CT	2 (2.2)
Fehrenbacher	Vallejo, CA	1 (1.1)
Garfield	Denver, CO	1 (1.1)
Goldberg/Franklin	Atlanta, GA	1(1.1)
Gordon	Dallas,TX	26 (29.2)
Granai	Providence, RI	10 (11.2)
Hainsworth	Nashville, TN	6 (6.7)
Kosty	La Jolla, CA	5 (5.6)
Lopez	Tucson, AZ	6 (6.7)
Malfetano	Albany, NY	4 (4.5)
Malviya	Southfield, MI	3 (3.4)
Moore	Decatur, GA	2 (2.2)
Orr	Ft. Myers, FL	1 (1.1)
Peters	Seattle, WA	4 (4.4)
Rose	Cleveland, OH	9 (10.1)
Weissman	Latham, NY	6 (6.7)
Wolin	Los Angeles, CA	1 (1.1)
Yee	Arcadia, CA	1 (1.1)
Total=18		Total=89 (100.0)

Reviewer comment: When the above referenced table and listing were compared, there were differences. The sponsor has been queried (4/6/99) about the differences. We are still awaiting a complete reply. The discrepancy should involve only a few (<5) patients.

8.2.4.2 Baseline Patient Characteristics

90 patients were enrolled, of which 89 actually received treatment. 1 patient withdrew consent before treatment was given and no further information was submitted about this patient.

Baseline demographics show that all patients were female, median age 61 (34-85) years. Ethnic distribution was 91% Caucasian, 8% black, and 1% Hispanic.

In terms of performance status, the ITT population's median KPS was 90% (range 60-100%) for 88 patients.. Median baseline cardiac ejection fraction was 63% (range 49-80%; mean 62.6%) for 85 patients.

Distribution by Stage at Diagnosis using ITT Population (v10,p17)

FIGO Stage	No. (%) of Patients
I	3 (3.4)
II	3 (3.4)
III	65 (73.0)
IV	18 (20.2)
Total	89 (100.0)

Distribution by Grade at Diagnosis using ITT Population (v10,p18)

Histologic Grade	No. (%) of Patients
Well Differentiated	1 (1.1)
Moderately Differentiated	5 (5.6%)
Poorly Differentiated	21 (23.6)
Grade Not Specified	62 (69.7)
Total	89 (100.0)

Since this is not a single-arm trial, only limited conclusions may be drawn from the above data. They appear to reasonably represent a population of advanced ovarian cancer patients.

8.2.4.2.1 Prior Therapy

Prior therapy recorded for this trial included radiotherapy and chemotherapy.

Three of the 89 ITTpatients received radiotherapy prior to enrollment to this study, 2 to the anterior and posterior pelvis, and one patient to the right axilla, supraclavicular area, and breast. (electronic table "tumradio")

By FDA analysis, 82 of the 89 patients comprising the ITT population met the inclusion criteria for disease progression either while receiving platinum- and taxane-based therapy, or within 6 months of their completion. The following table specifies why these criteria were not met

Patient ID	Last Platinum	Platinum Progression Date	Last Platinum-Progression	Last Taxane	Taxane Progression Date	Last Taxane-Progression
[redacted] (b) (6)			>3-1/3 yrs	[redacted] (b) (6)		>3-1/3 yrs
			> 9 mos			> 9 mos
			> 8 mos			> 8 mos
			> 8 mos			> 8 mos
			> 6 mos			> 6 mos
			> 7 mos			2 wks
			2-4 mos			> 10 mos
Total=7						

Of the 82 patients remaining in the ITT population that meet the eligibility criteria, the sponsor then subtracts a further subpopulation that has received only 1 cycle. This was NOT pre-specified in the protocol document. The reasons only one cycle of therapy was given varies, although most often it has to do with disease progression, or adverse events most likely due to tumor progression. Occasionally, a single cycle of therapy was given followed by severe AE judged probably due to study drug.

Reviewer comment: Clearly patients which receive only one cycle of therapy due to disease progression, disease-related AE's, or drug-related AE's will, as a group, have a lower response rate than the whole eligible ITT population. Thus, a significant bias is introduced by subtracting a poorer-responding population from the denominator and resulting in an increased response rate.

Within the eligible ITT population of 82, there is a subpopulation of patients accrued who had also received topotecan following the platinum- and taxane- based therapy. The specific duration or time from last topotecan therapy to progression is not specified in the protocol document. Thus, all patients in the eligible ITT population who had received topotecan following platinum- and taxane-based therapy were considered "triple refractory" for purposes of analysis. This population numbers 26 patients.

Again, the sponsor subtracts a subpopulation that only received a single cycle of DOXIL. As previously noted, the same bias is present here when the sponsor subtracts those patients receiving only one cycle. In the case of the triple refractory eligible ITT population, 3 patients are subtracted, leaving a denominator of 23.

8.2.4.3 Therapy Delivered

The ITT population of all 89 patients was used for FDA analysis of therapy delivered.

Data taken from electronic query "dose (mg/m2) by cycle" (will be removed before finalized)

Cumulative DOXIL by Number of Cycles and Number of Patients

No. Cycles	No. Patients	Range of Cumulative DOXIL (mg/m2)
1	17	50-52.33
2	26	87.5-100.62
3	8	124.84-153.06
4	2	175.96-187.47
5	4	239.15-254.56
6	8	264.21-300
7	6	277.99-355.27
8	5	337.38-401.58
9	4	399.93-450.3
10	4	420.02-500
11	3	500.52-550
12	0	--
13	1	569.38
14	0	--
15	0	--
16	1	808.42
	Total = 89	

FDA independent analysis of all administrations in electronic database "doseall" essentially parallels sponsor's analysis.

Of the 389 drug administrations, 118 (30.3%) required some alteration, either delay, interruption, or reduction. Thus, 271 (69.7%) were administered without any modification.

Another way to analyze these data is to determine the likelihood that sufficient toxicity will be encountered such that dose reduction and/or delay becomes necessary. Of the 89 patients in the ITT population, 32 (36%) completed 6 or more cycles. Of the 32 patients completing 6 or more cycles, 10 were able to complete the six cycles without toxicity necessary for dose reduction or delay, and 22 required either delay, reduction, or both. Of the 22 requiring reduction or delay, 9 required dose delay only, 4 required dose reduction only, and 9 required both reduction and delay.

8.2.4.3.1 Termination

The reasons underlying termination decisions are summarized in the table below, excerpted form the sponsor's study report (table 4, v10,p48/62).

Sponsor's Summary of Early Termination Reasons

Complete Protocol	7 (7.9)
Continuing Treatment	6 (6.7)
Adverse Event/Toxicity	15 (16.9)
Disease Progression	35 (39.3)
Lost to Follow-up	1 (1.1)
Death	7 (7.9)
Other	18 (20.2)
	Total = 89

Sponsor (v10, p18/32):

"Seven (7.9%) patients were noted to have completed the protocol by the investigator (trial completion was defined in the protocol as completing six cycles of DOXIL). Seventy-six (85.4%) patients terminated early from study: 35 (39.3%) due to disease progression, 15 (16.9%) due to adverse events, 7 (7.9%) patients died on study, 1 (1.1%) patient was lost to follow-up, and 18 (20.2%) patients terminated the study because of other reasons. Six (6.7%) patients are continuing on the trial. Of the 15 patients who discontinued due to adverse events, 7 patients were discontinued due to events considered unrelated to study drug; 3 patients were discontinued due to grade 3 PPE considered related to study drug; 1 patient each was discontinued for grade 4 stomatitis and neutropenia; 2 patients were discontinued for cardiotoxicity related to DOXIL (grade 3 and 1); and, 1 patient was discontinued for grade 3 asthenia."

Reviewer comment: The reasons cited in the table above reflects the "Study Completion" page in the CRF. In this form the following are choices: (1) study completed according to protocol, (2) study was prematurely discontinued because (a) adverse event, toxicity, or intercurrent illness, (b) progression of ovarian cancer, (c) non-compliance with drug or protocol schedule, (c) prohibited medication required, (d) inappropriate enrollment, (e) patient lost to follow-up, (f) patient died, (g) other.

Independent FDA evaluation of terminations of all 89 patients in the ITT population as denoted in the CRF's revealed the following summarized in the table below:

FDA Analysis of Reasons for Termination

Continuing on study	4
Progressive Disease	42
Physician Discretion	10
Adverse Events	12
Patient Request	11
Death on Study	6
Unclear	3
Lost to Follow-up	1
	Total = 89

The most prominent reason for early termination was progressive disease, comprising 43 (48.3%) of the total ITT population of 89. The second most common reason was adverse events, either due to study drug or disease, and this accounted for 12 (13.4%).
The third most common reason for early termination is patient request, comprising 11 (12.4%). The specific reason cited were often unclear, but in no case was there any patient who was responding well, or relatively free from toxicity. The fourth most common reason for early termination was physician discretion. Often, this was related to elevated CA-125.

Reviewer comment: With amendment #1 CA-125 was removed as a marker of measurable disease or disease progression. The subsequent 50 patients accrued to this study were not to have their measurable disease status or disease progression status influenced by CA-125 levels.

A number of patients were discontinued for reasons difficult to ascertain, but probably include moderate toxicity (such as grade 2 stomatitis), rising CA-125, and/or QOL factors not specifically measured.

8.2.4.4 Patient Follow-up and Disposition

The protocol specified that patients were to be followed until death. CRF forms indicated whether each patient was alive after terminating the study at 3, 6, 9, and 12 months. As of the data cutoff date 15 June 1998, 22 patients were in long-term follow up. Survival ranged from 8 -- 602 days. No toxic deaths attributable to DOXIL were found in the electronic database, and the company has confirmed they are unaware of any deaths associated with the administration of DOXIL.

8.2.4.5 Efficacy Evaluation

8.2.4.5.1 Sponsor's Evaluation of Efficacy

Sponsor (v10,p20/34):
"Efficacy results for this study are presented for the 89 patients who received DOXIL (intent-to-treat [ITT] population) and the 63 patients who received at least two cycles of therapy and had evaluation of tumor response (evaluable population). Additionally, efficacy results will be presented for the subgroup of patients who are refractory to both platinum and paclitaxel based on their previous treatment history (double-refractory patients). There are 82 double-refractory patients, 59 of whom were evaluable. Results were similar in the subsets of patients."

Sponsor (v10, p55/69):

TABLE 8a
SUMMARY OF ONSET AND DURATION OF INVESTIGATOR THERAPEUTIC RESPONSE
ALL PATIENTS FROM INTENT-TO-TREAT POPULATION

	DOXIL/CAELYX
Number of Patients	89
Responders:	15 (16.9%)
Complete	1 (1.1%)
Partial	14 (15.7%)
95% Confidence Interval for Responder Rate	(9.1%, 24.6%)

Sponsor (v10,p57/71):

TABLE 9a
SUMMARY OF ONSET AND DURATION OF INVESTIGATOR THERAPEUTIC RESPONSE
ALL PATIENTS FROM EVALUABLE POPULATION

	DOXIL/CAELYX
Number of Patients	63
Responders:	15 (23.8%)
Complete	1 (1.6%)
Partial	14 (22.2%)
95% Confidence Interval for Responder Rate	(13.3%, 34.3%)

Reviewer comment: The sponsor in the above paragraph uses a definition of "evaluable" for patients that received two or more doses of DOXIL. This is a *post hoc* definition, and not specified in the protocol document. Its effect is to exclude from the ITT population a less responsive subpopulation, thereby increasing the apparent response rate.

Reviewer comment: The sponsor defines a double-refractory population, and later defines a triple-refractory population. Per the protocol document, there is no prospective definition of either population. Instead, by application of the eligibility criteria, the population under study is, by definition, double-refractory.

Sponsor (v10, p22/36):
"For the double-refractory patients, the median time to response for those patients who responded and the median duration of response was the same as above. The median time to progression for all evaluable double-refractory patients was 188 days (26.9 weeks), with a range of 49 to 501 days (7 to 71.6 weeks) (Table 9b). The median time to progression for the ITT double-refractory patients was 119 days (17 weeks), with a range of 5 to 501 days (0.7 to 71.6 weeks) (Table 8b)."

TABLE 8b
SUMMARY OF ONSET AND DURATION OF INVESTIGATOR THERAPEUTIC RESPONSE
DOUBLE AND TRIPLE REFRACTORY PATIENTS FROM INTENT-TO-TREAT POPULATION

	DOXIL/CAELYX
For Responders Only:	
Time to Response (Days)	
N	15
Median	106
Range	23 to 230
Duration of Response (Days)	
N	15
% Censored	40.0
Median	169
Range	32+ to 338
For All Patients:	
Time to Progression (Days)	
N	82
% Censored	20.7
Median	119
Range	5 to 501

8.2.4.5.2 Reviewer's Evaluation of Efficacy

FDA analysis centered on identifying the platinum- and taxane-refractory ITT population as the denominator for the response rate calculation. A smaller subpopulation of "triple-refractory" eligible ITT patients was used as the denominator for determining the "triple-refractory" response rate.

FDA analysis of response started with the electronic database table "aomdfile." Cross-sectional areas calculated from serial tumor measurements, summed, and were then compared to the baseline total cross-sectional area. The protocol-specified criteria for response, stable disease, and progressive disease were applied. All 89 patients in the ITT population underwent this analysis, and their "refractory" status was determined separately.

Reviewer comment: FDA reviewers applied standard criteria for verification of tumor response. An unverified response is likely not to be of value as a surrogate for clinical benefit.

FDA analysis reveals 14 responses (13 PR and 1 CR) in the eligible ITT population of 82 patients, with a calculated response rate of 14/82 or 17.1% (exact 95% CI 9.7 – 27.0%). The exact 95% CI was calculated under the assumption of a binomial distribution. Two responses (2 PR) were found in a sponsor-defined subpopulation of 26 patients who also received topotecan. This yields a "triple refractory" response rate of 7.7% (exact 95% CI 0.9 – 25.1%).

Secondary Endpoints in Responding Patients

Patient ID	R	Start of DOXIL therapy	Date of Response ("aomdfile")	Date of Relapse ("aomdfile")	Date of Death (CRF)	TTR	DOR	Surv
(b) (6)	PR				(b) (6)	84	68	387
	PR					86	230	450
	PR					433	35	561
	PR					227	31	299
	CR					76	83	338
	PR					174	0	200
	PR					112	69	666
	PR					144	118	324
	PR					123	150	364
	PR					95	332	436
	PR					102	50	249
	PR					194	49	418
	PR					136	117	328
	PR					56	75	131
Total=14								

Included in sponsor's evaluation of efficacy is a two paragraph discussion about CA-125.

Sponsor (v10,p24/38):
"The median CA-125 at baseline was 210.5 U/mL; mean was 1794.76 U/mL; range was 7 to 46,594 U/mL. As indicated by the broad range of values, there was considerable variability among patients, and no clear trend was evident to link changes in CA-125 levels to the therapeutic response."

Reviewer comment: No claims are made about the efficacy of DOXIL in ovarian cancer using CA-125 as a surrogate.

Reviewer comment: Included also in sponsor's study report is a discussion about quality of life (QOL) as determined from an HQL instrument. This portion of the study was included by Amendment #1dated 14 January 1997 after 39 patients had accrued to the trial. Following is an excerpt of sponsor's discussion in the study report.

Sponsor (v10,p24/38 and 27/41):
"Thirty-nine of 89 patients were enrolled before the first protocol amendment; therefore the pretreatment HQL assessment is not available for these patients. For the 50 patients who were enrolled after the first protocol amendment, 34 completed the pretreatment HQL questionnaire and had at least one HQL assessment after baseline (cycles 1 - 8). These 34 patients are included in the analysis."

"Due to small sample size and progressive patient withdrawal, the results from this analysis are difficult to interpret."

Reviewer comment: The capture of QOL data in this trial is fraught with difficulties and biases, from which little meaningful results may be drawn. First, of the 89 patients in the trial, only 34/89 (38.2%) completed the baseline questionnaire and one form with at least one subsequent cycle. Thus it is difficult to consider the attempt at QOL determination to be anything much more than non-random sampling. To be sure, the sponsor did not prospectively declare that any of the data from this survey would be used for efficacy claims, but stated instead that the QOL component was intended for the sponsor to "gain experience using QOL instruments." Also, the sponsor correctly calls attention to the bias inherent in querying patients over multiple cycles, which would tend to make the drug appear more favorable in terms of quality of life.

8.2.4.6 Analysis of Safety

8.2.4.6.1 Deaths

Sponsor (v10,p28/42):
"For 7 (7.9%) of the 89 patients, the reason for termination from the study was death. Each of these deaths was attributed to progressive disease. None of the deaths was considered related to study drug. There have been 46 (51.7%) deaths on study. Forty-five were due to disease progression, 1 was attributed to a complication of surgery to relieve a bowel obstruction. The median survival time for all patients (censored for 48.3% of patients) was 329 days (47 weeks) from the time of first DOXIL dose, with a range of 8 to 602 days (1.1 to 86 weeks)."

FDA Analysis of Reasons for Termination

Continuing on study	4
Progressive Disease	41
Physician Discretion	10
Adverse Events	12
Patient Request	11
Death on Study	7
Unclear	3
Lost to Follow-up	1
	Total = 89

Of the seven deaths on study by FDA analysis, five were due to progressive disease, one case is attributable to DOXIL, and one is unclear. Regarding patient (b) (6) the cause of death is unclear. Although the investigator indicates progressive disease, the patient experienced grade 4 thrombocytopenia 4 days prior to death despite being recorded as having a KPS of 90% one week before death. The proximate cause of death for patient (b) (6) was bowel obstruction, probably due to progressive disease. Patient (b) (6)'s cause of death is less clear. Patient was on study 8 days and received one cycle of DOXIL of uncertain dose. According to the CRF, 50 mg/m2 was administered, although the electronic table "doseall" states that 128.1 mg/m2 was infused. The sponsor is currently reconciling these findings. The cause of death in patient (b) (6) was neutropenic sepsis, and probably is **related to study drug**. The patient's dose had been had been previously reduced and delayed for myelosuppression, and she had been receiving Neupogen. Patient (b) (6) likely died of disease progression complicated by deep venous thrombosis, small bowel obstruction, and dehydration. A pulmonary embolus was the cause of death in patient (b) (6), and small bowel obstruction was the proximate cause of death stemming from progressive ovarian cancer in the case of patient (b) (6).

8.2.4.6.2 Serious Adverse Events

Sponsor (v10,p28/42):
"A total of 33 (37.1%) patients experienced one or more serious adverse events during the study. Eleven of these patients had events that were judged as possibly or probably related to the study drug."

Reviewer comment: The precise definition of what an SAE actually is comprised of is unclear, and the reviewer did not locate it in either the protocol document or in the study report. Thus, some differences between the medical reviewer's analysis and sponsor's may be attributed to this.

FDA Analysis

The reviewing medical officer's definition of an SAE was either grade 4 hematologic toxicity OR grade 3 or 4 non-hematologic toxicity. In a few cases, the QOL questionnaire was useful in further determining the severity of an AE.

Review of the AE's included review of all AE's for each patient from the electronic database "aemax". This was supplemented by review of the CRF's as felt necessary to further understand the clinical condition, concomitant medications, etc. In general, there was good concordance between the table "aemax" and the source of the information for this table from the CRF's.

Each patient's case was reviewed for spectrum of toxicities experienced along with the maximum grade of each AE. This was combined with data about dose delay and dose reduction in an effort to review adherence to protocol specifications as well as to glean an overall perspective of the management of each patient.

Of the 89 patients in the ITT population, 65/89 (73.0%) experienced an SAE. Of the 65 patients experiencing a SAE, 52 (52/89 =58.4%) were attributable to DOXIL administration and 13 (13/89=14.6%) were attributable to ovarian cancer or other underlying co-morbidity.

8.2.4.6.3 AE-Specific Analysis

8.2.4.6.3.1 Cutaneous Toxicity (PPE,HFS)

Characteristic of DOXIL is the associated cutaneous toxicity which manifests itself in multiple ways, and is described by different terms including palmar-plantar erythrodysesthesia (PPE), hand-foot syndrome (HFS), vesiculobullous rash, exfoliative dermatitis, and pruritis.

In addition, toxicity to the mucous membranes appears to be associated with study drug. Several names for this adverse event include: mucositis, stomatitis, esophagitis and dysphagia unattributable to any other etiology.

Sponsor (v10,p32/46):

"Thirty-seven (41.6%) patients experienced PPE, and all were considered probably or possibly related to treatment, making PPE the most frequently reported event with a possible relationship to DOXIL. Three patients ((b) (6), (b) (6), (b) (6)) withdrew from the study because of grade 3 PPE."

"Dosing with 50 mg/m^2 every 4 weeks resulted in severe PPE in 18 (20.2%) patients, moderately severe PPE in 10 (11.2%) patients and mild PPE in 9 (10.1%) patients. Because of PPE, 19 patients required dose delays and 15 patients required dose reductions. The number of doses delayed and/or reduced per cycle is shown in the following tally (see Table 6 for numbers of patients per cycle and numbers of patients with dose modifications, i.e., dose delayed, interrupted, or reduced)."

	Cycle								
	1	2	3	4	5	6	7	8	9
No. of patients:									
total ITT	89	72	46	38	36	32	24	18	13
with dose modifications	3	14	15	15	12	14	15	9	10
Number of doses:									
delayed due to PPE		2	4	8	5	3	2	2	1
reduced due to PPE		2	1	4	2	1	3	2	0

"Skin rashes occasionally extended beyond palmar and plantar areas, such as over the shins (in sun-damaged areas) or along intertriginous folds. Twenty-six patients (29.2%) experienced rash; for 3 (3.4%) patients the event were grades 3 or 4. One (1.1%) patient required a dose reduction in cycle 4. Vesiculobullous rash was documented in 9 (10.1%) patients. Exfoliative dermatitis was documented in 1 (1.1%) patient; this event was severe."

Reviewer comment: FDA analysis essentially confirms sponsor's above claims about cutaneous toxicity. FDA medical review grouped the following terms under **cutaneous toxicity**: "exfoliative dermatitis", "vesiculobullous rash", "hand-foot syndrome" "rash" "pruritis" and "palmar-plantar dysesthesia."

8.2.4.6.3.2 Mucositis

Sponsor's analysis of mucous membrane disorder is excerpted below (v10,p33/47):

"31 (34.8%) patients experienced stomatitis. All stomatitis events were considered related to study drug, and for 8 (9%) patients the event was grade 3 or 4. Six patients required

dosing delays because of stomatitis. Three patients required delays in cycle 3; and 1 patient each required delays in cycles 2, 6 and 7 for stomatitis. Two patients required dose reductions for stomatitis, one in cycle 6 and one in cycle 3. The latter patient also required a 10% dose reduction in cycle 5."

"Nineteen (21.3%) patients experienced mucous membrane disorder, mucositis. All mucositis events were considered related to DOXIL, and 5 (5.6%) were severe. Vesiculobullous rash was documented in 9 (10.1%) patients. Exfoliative dermatitis was documented in 1 (1.1%) patient; this event was severe. Four (11.4%) patients experienced mucous membrane disorder; all events were considered related to study drug."

Reviewer comment: FDA analysis, which used several terms as synonyms for mucous membrane toxicity (mucositis, stomatitis, esophagitis and dysphagia unattributable to any other etiology) essentially confirmed sponsor's claims above.

8.2.4.6.3.3 Infusion Reactions

Infusion-related reactions required interruption or termination of the infusion dose. Excerpted below is the sponsor's assessment of the nature and frequency of infusion-related reactions (v10, p33/47):

"Four (4.5%) patients had infusions of DOXIL interrupted because of an acute infusion reaction. Patients (b) (6), (b) (6), and (b) (6) experienced infusion reactions associated with their 1st infusion of DOXIL. All continued on study and received repeat doses of DOXIL without recurrence of symptoms. Patient (b) (6) experienced an infusion reaction with her 2nd infusion of DOXIL. The dose was interrupted because of this, and she was subsequently removed from study for progressive disease without receiving more DOXIL."

Reviewer comment: FDA review reveals essentially the same findings as sponsor indicates.

Cardiotoxicity

Concern over potential anthracycline-related cardiotoxicity prompted the sponsor to require LVEF's by MUGA in all patients at baseline and after cycle 6.

The paragraph below is excerpted from the sponsor's analysis of cardiac events and potential cardiotoxic effects of DOXIL. (v10,p34/48)

"In terms of cardiotoxicity observed during DOXIL therapy, several different signs and symptoms probably or possible of cardiac etiology were noted. One case of grade 5 heart failure was judged unrelated to study drug. Anecdotal observations of arrhythmia, bundle branch block, one case of congestive heart failure, and two cases of grade 2 tachycardia were judged unrelated to study drug. Four cases of myocardial toxicity including diminished ejection fraction and left ventricular enlargement were deemed related to DOXIL, although 11 cases of chest pain were mostly not attributable to study drug."

8.2.4.6.4 Hematologic Toxicity

Hematologic toxicity was monitored by frequent CBC's and dose reduction, delay and supportive care (growth factors, antibiotics, transfusions) were allowed per protocol as needed. The sponsor's analysis and FDA medical officer analysis appear below for each of the three hematopoietic lineages.

8.2.4.6.4.1 Anemia

Sponsor (v10,p36/50):

"Anemia was reported for 37 (41.6 %) patients; it was mild in 9 (10.1%), moderate in 16 (18.0%), and severe in 12 (13.5%) patients. Anemia was considered by investigators to be probably or possibly related to treatment in 35 (39.3%) patients. Three patients ((b) (6), (b) (6), (b) (6)) received epoetin alpha. Two of these patients had associated moderately severe anemia: (b) (6), (b) (6) (during cycles 12 and 5, respectively). Patient (b) (6) who had a hemoglobin of 13 g/dL on study day 7 received epoetin alpha in the first cycle at the discretion of the investigator. Ten patients received packed RBC transfusions. Seven patients received single transfusions, while 3 patients had from 2 to 5 transfusions each. Listing 20 provides details."

Reviewer comment: FDA essentially confirms sponsor's analysis. Although it appears that DOXIL causes anemia, this AE is generally easily remediable, and except for time and expense involved, the medical risk of this AE is quite small.

8.2.4.6.4.2 Thrombocytopenia

Sponsor (v10,p36/50):
"Thrombocytopenia was reported in 9 (10.1%) patients; it was mild in 7 (7.9%), severe in 1 (1.1%), and life threatening in 1 (1.1%). The occurrence of thrombocytopenia was considered by the investigators to be related to treatment in 8 of the 9 patients. No patients received platelet transfusions."

Reviewer comment: No cases of worsened morbidity stemming from low platelets were found in review of the electronic data and CRF's. Thus, it appears to be somewhat uncommon AE, with severe or life-threatening potential in a small minority of drug

administrations. No transfusions of platelets were found in the "trnsfuse" electronic data table. FDA analysis agrees with sponsor's analysis.

8.2.4.6.4.3 Neutropenia/Leukopenia

Sponsor (v10,p35/49 and 36/50):
"Neutropenia was reported in 37 (41.6%) patients; 33 (37.1%) of the patients' neutropenia were considered possibly or probably related to study drug. The event was graded as mild in 13 (14.6%) patients, moderate in 9 (10.1%), severe in 10 (11.2%) and life-threatening in 5 (5.6%). Four patients ((b) (6), (b) (6), (b) (6), (b) (6)) received CSFs during the trial, all of which experienced severe (grade 3 or 4), related neutropenia."

"Leukopenia was reported as an adverse event for 38 (42.7%) patients; for 35 (39.3%) patients the event was considered possibly or probably related to DOXIL treatment. Leukopenia was graded mild in 15 (16.9%) patients, moderate in 16 (18.0%), severe in 6 (6.7%), and life-threatening in 1 (1.1%) patient."

"Two patients had fever associated with neutropenia; both were considered serious adverse events by the investigator (see Section 8.1.2)."

- Patient (b) (6) was admitted with neutropenia and fever 13 days after her first dose of DOXIL. The patient was diagnosed to have an urinary tract infection.
- Patient (b) (6) was hospitalized for evaluation of severe erythema and blistering of feet, hands and palms 16 days after her third cycle of DOXIL. Several days prior to admission, the patient experienced increasing erythema, warmth and pain involving the hands, feet and right lateral thigh; erythema was also noted in the left axilla. One day prior to admission, the patient noted blistering and desquamation of the hands and palms. She also experienced chills and a questionable fever of 100.4 °F. The patient's CBC before this episode indicated grade 4 neutropenia. The patient was treated with antibiotics, pending blood cultures, and with topical therapy for rash and oral pain management. The condition of the patient was unchanged. The investigator indicated that the event was probably related to the study drug.

"Eleven (12.4%) patients had dose delays because of hematologic toxicity. Patient (b) (6) had a delay because of grade 2–3 leukopenia and neutropenia in cycles 2 to 10, (b) (6)

had grade 3 neutropenia in cycle 2, (b)(6) had grade 1–2 leukopenia and neutropenia in cycle 2, (b)(6) had grade 1–2 leukopenia and neutropenia in cycles 2 to 9, (b)(6) had grade 2 anemia in cycle 13, (b)(6) had grade 2–4 leukopenia and neutropenia, (b)(6) had grade 1 neutropenia, (b)(6) had grade 2 neutropenia in cycles 4 to 10, (b)(6) had grade 3 neutropenia in cycles 2 to 6, (b)(6) had grade 1–4 leukopenia and neutropenia and patient (b)(6) had a dosing delay in the second cycle because of hematologic toxicity."

Reviewer comment: FDA review of sponsor's submitted electronic data essentially confirms sponsor's summarized findings above. The more significant hematological parameter, however, is neutropenia, given its well-known relationship to risk of infection. Sponsor has clearly outlined the cases where neutropenia, presumably caused by DOXIL, has resulted in adverse outcomes. These cases have been reviewed by FDA and mirrors sponsor's findings.

In summary, DOXIL appears to have modest myelosuppressive potential, which on occasion manifests itself as severe to life-threatening cytopenias of the granulocytic and megakaryocytic lineages.

8.2.4.6.5 Gastrointestinal Toxicity

Sponsor (v10, p36/50):

"Nausea was the most commonly reported adverse event experienced by 54 (60.7%) patients, although for only 34 (38.2%) patients, the nausea was considered possibly or probably related to study drug; for 14 (15.7%) of these patients, the nausea was grade 3 or 4. Vomiting was experienced by 36 (40.4%) patients. For 17 (19.1%) patients, the vomiting was considered possibly or probably related to study drug; for 14 (15.7%) patients, the vomiting was severe. Antiemetic agents were frequently used."

Reviewer comment: Sponsor's findings are essentially confirmed. Review of the attribution in electronic table "aemax" and the CRF's clearly indicates study drug is causal in many cases, but that progression of ovarian cancer, manifesting itself as bowel obstruction or worsening ascites, was responsible for many cases as well. It is also clear that concomitant administration of members of several classes of antiemetics effectively mitigate against the emetigenic nature of DOXIL.

Diarrhea was listed occasionally in "aemax." Sponsor finds (v10, p36/50):

"Diarrhea was experienced by 20 (22.5%) patients. For 11 (12.4%) patients, the diarrhea was considered possibly or probably related to study drug; it was severe in 3 (3.4%) patients."

Reviewer comment: FDA analysis essentially confirms these findings.

Another AE seen in association with DOXIL is asthenia. Sponsor briefly mentions this in the study report (v10 ,p36/50):

"Forty-four (49.4%) patients developed asthenia. For 37 (41.6%) of these patients, the asthenia was considered possibly or probably related to study drug."

Reviewer comment: Asthenia is the most common adverse event attributable to DOXIL, and this analysis, while essentially confirmed by FDA medical reviewer, required further inquiry. Similar COSTART terms found in table "aemax" include "asthenia" "myasthenia" and "malaise". In total, 79 cases of any grade of asthenia were noted in 389 administrations of study drug, or 20.3%. Of the 79 cases, there were no grade 4 events recorded, and 13 events of grade 3 severity (13/79 or 16.5%). Virtually all events were judged to be related to study drug.

8.2.4.6.6 Serum Chemistries

Sponsor (v10, p37/50):

"A summary of maximum alkaline phosphatase, AST, total bilirubin and serum creatinine values is found in Table 19. Most maximum alkaline phosphatase and AST values remained near normal; mean maximum alkaline phosphatase and AST were 160.8 IU/L (range, 43 to 1976) and 34.4 IU/L (range of 11 to 446), respectively. The changes in alkaline phosphatase and AST values were not clinically significant. For alkaline phosphatase, the median changes from baseline to end of each cycle and end of treatment ranged from a decrease of 1.3% at end of cycle 2 to an increase of 7.8% at end of cycle 6, with a median increase of 7.6% at the end of treatment (Table 24). For AST, the median changes from baseline to end of each cycle and end of treatment ranged from 0% at end of cycle 1 to an increase of 14.3% at the end of treatment (Table 25). The alkaline phosphatase and AST levels are summarized by cycle in Table 30."

"Most maximum total bilirubin and serum creatinine values remained near normal. Mean maximum total bilirubin and serum creatinine were 0.69 mg/dL (range, 0.2 to 8.1) and 1.17 mg/dL (range of 0.3 to 14.0), respectively. No trends developed to suggest that DOXIL administration affected hepatic or renal parameters. There were no median changes from baseline to end of each cycle (1 to 6) and end of treatment for total bilirubin (Table 26), nor for serum creatine (Table 27). The total bilirubin and AST serum creatinine levels are summarized by cycle in Table 31."

Reviewer comment: Sponsor's findings above are essentially confirmed. In terms of serum chemistry abnormalities, medical officer visual inspection of most patients' values on a cycle by cycle basis revealed no significant trends or striking findings, with the exception of anecdotal moderate abnormalities.

8.2.4.7 Summary of Safety Review

Sponsor has summarized the relative frequency of each of the principal adverse events discussed above (v10, p32/46):

Adverse Event	% of patients
Asthenia	41.6%
PPE	41.6%
Leukopenia	39.3%
Anemia	39.3%
Nausea	38.2%
Neutropenia	37.1%
Stomatitis	34.8%
Rash	28.1%
Mucous membrane disorder	21.3%
Vomiting	19.1%
Anorexia	13.5%
Diarrhea	12.4%

In summary, the toxicity of DOXIL administered at 50mg/m2 intravenously every four weeks appears to cause cutaneous toxicity in the form of hand-foot syndrome and mucositis. In addition, there is frequent moderate and occasionally severe hematologic toxicity following DOXIL administration, sometimes requiring dose delay or reduction, and rarely resulting in neutropenic fevers and infections. Red cell transfusions were occasionally required, although platelet transfusions were not necessary for DOXIL induced myelosuppression.

Summary of Medical Officer's Review of Study 30-47

DOXIL has been studied in the platinum-and taxane-refractory ovarian cancer population. The primary efficacy endpoint was specified as response rate and 14 confirmed responses (including 2 CR's) were confirmed by FDA out of 82 patients confirmed by FDA to be refractory to both classes of agents, leading to a response rate of 17.1%. In the "triple refractory" population a 7.7% response rate (including 1 CR) was observed. Secondary efficacy endpoints included TTR, DOR, TTP and survival. Twenty-two of the 32 (69%) patients completing at least six cycles of DOXIL required either dose reduction, dose delay, or both. Grade 4 hematological and grade 3 and 4 non-hematological toxicities were encountered by 58% of the patients on the study which could be attributed to DOXIL. Specific adverse events necessitating delay or reduction in DOXIL administration included **cutaneous toxicity**, **mucous membrane toxicity**, myelosuppression resulting in **anemia** infrequently requiring transfusions, **thrombocytopenia** without hemorrhagic sequelae and not requiring transfusions, and **leukopenia/neutropenia** resulting in infrequent febrile neutropenia but with one case of neutropenic sepsis resulting in death.

8.3 Study 47E

A Noncomparative, Multicenter Study of DOXIL/CAELYX in the Treatment of Patients with Advanced Epithelial Ovarian Carcinoma

8.3.1 Location of information reviewed in NDA:

Study Item	Volume
Study Report	18-21
Protocol	19 (pp. 1-55)
Amendments	11 (pp. 56-71)
Listings	20-21
CRF's	Vols. 1-12 (2/24/99 submission)
Database documentation	"dox3047e.mdb"
Integrated Summary of Efficacy	48

8.3.2 Important Study Dates

Study Period	July 1996 – June 1998
First Patient's First Treatment	October 1996
Last Patient's First Treatment	June 1998

8.3.3 Review of protocol and amendments

NOTE: This study protocol is identical to the study protocol for study 30-47. Many references will be made to the study 30-47 to streamline this review. Areas that will be reviewed independently include study conduct and evaluation of safety.

8.3.3.1 Protocol Amendments

Please refer to study 30-47 protocol review.

8.3.3.2 Investigators

This is a multi-center European study involving 14 investigators. The three highest-accruing investigators are listed with their study site and accrual. (v18,p13-14)

Gore	Royal Marsden Hospital, London	13 patients
Huinink	Netherlands Cancer Institute, Amsterdam	10 patients
Verweij	Rotterdam Cancer Institute, Rotterdam	6 patients

Note: all other sites accrued 4 or less patients.
(v20, p2)

8.3.3.3 Objectives

There are 2 objectives to this protocol

1. To describe objective response rates, time to response, duration of response, time to progression, and survival in patients with locally advanced or metastatic epithelial ovarian carcinoma who are refractory to platinum- and taxane-based chemotherapy and who have failed topotecan chemotherapy.

2. To assess the safety of DOXIL in this patient group. (v19,p5)

8.3.3.4 Rationale (see v11, p12)

Please refer to the review of study 30-47.

8.3.3.5 Inclusion/Exclusion Criteria

Please refer to the review of study 30-47.

8.3.3.6 Formulation

Please refer to the review of study 30-47.

8.3.3.7 Experimental Controls

This is a single-arm noncomparative multi-center domestic European study with no pre-specified stratification. There is no control arm.

8.3.3.8 Dosage Schedule

Please refer to the review of study 30-47.

8.3.3.9 Follow-up Details

Refer to the Applicant's follow-up schema below. Patients with meeting response criteria for a PR or CR were rescanned 2 months after the final cycle of DOXIL.

Activity	Pre-Treatment	During Treatment				After Treatment	Follow-up
	≤ 7 days pre-Study	Day 1	Weekly	Every Cycle	Every 8 Weeks (2 cycles)	End of Treatment (4 weeks after last dose)	2 mos after end of final cycle (pts with PR or CR)
Informed Consent	X						
Medical History	X						
Physical Examination	X			X		X	
Radiological Assessment	X				X		
MUGA/Echo	X						
ECG	X						
Hematology	X		X	X		X	
Serum Chemistry	X			X		X	
Serum CA 125	X					X	
Serum pregnancy	X						
Urinalysis	X					X	
CAELYX Administration		X					
Record Concomitant Meds		X	X		X	X	
Monitor Adverse Events		X	X		X	X	
Survival							X

(v19, p7; v18,p23)

8.3.3.10 Removal From Study

Please refer to the review of study 30-47.

8.3.3.11 Efficacy Considerations

Please refer to the review of study 30-47.

8.3.3.11.1 Response Criteria

Please refer to the review of study 30-47.

8.3.3.12 Safety Considerations

Please refer to the review of study 30-47.

8.3.4 Analysis of Study 47

8.3.4.1 Details of trial conduct and analysis

This was a multicenter European study with 52 patients enrolled at 149 sites. The data submitted to FDA accrued between October 1996 and June 1998, although the study is still ongoing. Three sites accounted for half the patients in the study; 13 in London, 10 in Amsterdam, and 6 in Rotterdam. (v20, p2)

Investigators and Distribution of Enrolled Patients by Trial Center

Investigator	Location	No. (%) of Patients
Bauknecht	Freiburg, Germany	2 (3.8)
De Greve	Brussels, Belgium	1 (1.9)
Gore	London, UK	13 (25.0)
Harper	London, UK	2 (3.8)
Huinink	Amsterdam, Netherlands	10 (19.2)
Karp	London, UK	1 (1.9)
Kaufmann	Frankfurt/Main, Germany	3 (5.8)
Osborne	Poole, Dorset, UK	3 (5.8)
Parkin	Foresterhill, Aberdeen, UK	3 (5.8)
Piccart	Brussels, Belgium	1 (1.9)
Thomas	London, UK	4 (7.7)
van Oosterom	Leuven, Belgium	1 (1.9)
Vasey	Glasgow, UK	2 (3.8)
Verweij	Rotterdam, Netherlands	6 (11.5)
		Total=52

8.3.4.2 Baseline Patient Characteristics

52 patients were enrolled, all of which received treatment.

Baseline demographics show that all patients were female, median age 52 (range 22 - 80) years. Ethnic distribution was 94.2% white, 1.9% Asian, and 3.8% "other." (v18,p14/31)

In terms of performance status, the ITT population's median KPS was 90% (range 60-100%) for 51 patients.. Median baseline cardiac ejection fraction was 63% (range 40-82%; mean 61.2%) for 47 patients.

Distribution by Stage at Diagnosis using ITT Population (table "dxhist)

FIGO Stage	No. (%) of Patients
I	5 (9.6)
II	1 (1.9)
III	36 (69.2)
IV	9 (17.3)
Not stated	1 (1.9)
Total	52 (99.9)

Distribution by Grade at Diagnosis using ITT Population (v18,p32)

Histologic Grade	No. (%) of Patients
Well Differentiated	1 (1.9)
Moderately Differentiated	8 (15.4%)
Poorly Differentiated	17 (32.7)
Grade Not Specified	26 (50.0)
Total	52 (100.0)

Reviewer comment: Since this is a single-arm trial, only limited conclusions may be drawn from the above data. They appear to reasonably represent a population of advanced ovarian cancer patients.

8.3.4.2.1 Prior Therapy

Prior therapy recorded for this trial included radiotherapy and chemotherapy.

4 of the 52 ITTpatients received radiotherapy prior to enrollment to this study, 2 to the pelvic area, one to the paraaortic area, and one patient to an unspecified area (table "tumradio").

8.3.4.3 Therapy Delivered

The ITT population of all 52 patients was used for FDA analysis of therapy delivered.

Data taken from electronic query "dose (mg/m2) by cycle" (will be removed before finalized)

Cumulative DOXIL by Number of Cycles and Number (%) of Patients

No. Cycles	No. Patients (%)	Range of Cumulative DOXIL (mg/m2)
1	12 (23.1)	48.78-50
2	19 (36.6)	97.56-102.7
3	7 (13.5)	137.97-150.87
4	2 (3.8)	200
5	3 (5.8)	212.5-251.2
6	8 (15.4)	247.96-301.65
7	0	--
8	1 (1.9)	333.35
	Total = 52	

FDA independent analysis of all administrations in electronic database "doseall" essentially parallels sponsor's analysis

Of the 150 drug administrations, 27 (18.0%) required some alteration, either delay, interruption, or reduction. Thus, 123 (82.0%) were administered without any modification.

Another way to analyze these data is to determine the likelihood that sufficient toxicity will be encountered such that dose reduction and/or delay becomes necessary. Of the 52 patients in the ITT population, 9 (17.3%) completed 6 or more cycles. Of the 9 patients completing 6 or more cycles, 4 were able to complete the six cycles without toxicity sufficient for dose reduction or delay (of 1 week or greater), and 5 required either delay, reduction, or both. Of the 5 requiring dose reduction or delay, 4 required dose delay only, 0 required dose reduction only, and 1 required both reduction and delay.

Summary of Abbreviated Review of Study 30-47E

Study 30-47E is the third study of DOXIL in platinum- and taxane-refractory ovarian cancer. Virtually identical in design to study 30-47, its primary endpoint was response rate. At the time of data cutoff, fifty-two patients were enrolled, and there were no responses observed in the 36 patients refractory to both platinum- and paclitaxel (exact 95% CI 0.0 – 9.7%) Factors which might explain the unexpectedly low response rate observed in this study were investigated by the applicant. Among the findings included higher mean CA-125 at study entry, younger meadian age (by about 8 years). Thus, younger patients with more aggressive disease, and possibly more poorly differentiate disease expressing higher levels of CA-125 may have less likelihood of response. The factors considered above, however, have not been investigated further and have not been determined on a prospective basis, nor do they completely explain the zero response rate.

8.4 Study 49

A Phase III, Randomized, Open-Label, Comparative Study of DOXIL®/CAELYX™ versus Topotecan HCl in Patients with Epithelial Ovarian Carcinoma Following Failure of First-Line, Platinum-Based Chemotherapy

Interim results from this study were submitted at the request of the agency to accompany studies 30-22, 30-47, and 30-47E. These interim results are intended to serve a supportive role in evaluating the response rate of DOXIL in patients refractory to platinum and paclitaxel.

8.4.1 Location of information reviewed in NDA:

Study Item	Volume
Study Report	40-46
Protocol	41 (pp. 1-79)
Amendments	41 (pp. 80-87)
Listings	43-46
CRF's	68-71
Database documentation	"Dox3049.mdb"
Integrated Summary of Efficacy	48

8.4.2 Important Study Dates

Study Period	May 1997 – June 1998 (v7,p3)
First Patient's First Treatment	5 May 1997 ("doseall")
Last Patient's First Treatment	Accrual cutoff 26 October 1998
	Data cutoff 26 October 1998 (study ongoing)
	Data cutoff 15 June 1998 (v40,p14/35)

8.4.3 Review of protocol and amendments

8.4.3.1 Protocol Amendments

Amendment #A 26 August 1997 (v40,p34)

Echocardiography was allowed on a site-specific basis in the cases where MUGA was unavailable. Two of 72 sites were affected.

Amendment #1 8 December 1997

This amendment modified the criteria for assessing the relationship of the study drug to an adverse event from "Probably Related", "Possible Related", and "Probably Not Related" to "Related", "Not Related" and "Unknown."

8.4.3.2 Investigators

This is a multicenter North American and European study involving 72 investigators. (v47,p2, Interim Efficacy Report dated 20 November 1998). The Interim Safety Report dated 24 November 1998 (v40,p5/26) indicates there are 45 study investigators, of which 23 are US and 22 are European. No reference to 2 Canadian investigators is made.

8.4.3.3 Objectives

The single objective of this study is to compare the safety and efficacy of DOXIL®/CAELYX™ versus topotecan HCl in patients with epithelial ovarian carcinoma following failure of first-line, platinum-based chemotherapy.

8.4.3.4 Rationale

Liposomal encapsulation of doxorubicin may overcome p-glycoprotein-mediated cellular resistance. Activity in ovarian cancer was noted in the phase I trial. Further evidence of activity has been noted in two phase II trials, although of different schedules.

8.4.3.5 Inclusion/Exclusion Criteria

Histologically proven epithelial ovarian carcinoma with FIGO staging classification

Measurable or Measurable and Evaluable disease, based on the following:

Measurable disease: bidimensionally measurable lesions with clearly defined margins by:

Plain x-ray with at least one diameter ≥ 0.5cm
(bone lesions not included)
OR
CT, MRI, or other imaging scan with both diameters ≥ 2 cm
OR
Palpation with both diameters ≥ 2 cm

Evaluable disease, having any one of the following:

Unidimensionally measurable lesions
OR
Masses with margins not clearly defined
OR
Lesions with both diameters less than or equal to 0.5 cm
OR
Lesions on scan with either diameter smaller than the distance between cuts
OR

Palpable lesions with either diameter less than or equal to 2 cm
OR
Malignant ascites OR pleural effusion in conjunction with serum levels of CA-125 > 100 U/mL in the absence of cirrhosis.

Nonevaluable disease: Pleural effusions, ascites, disease documented by indirect evidence only (e.g. serum tumor markers or other lab values) (v41,p23/33)

Recurrence of disease or disease progression indicative of failure of first-line platinum based chemotherapy.

KPS ≥ 60%

Age ≥ 18 y/o

Labs: ANC ≥ 1,500/uL **AND** Plts > 100,000/uL **AND** Hgb ≥ 9g/dL

Labs: Cr ≤ 2.5 mg/dL

Labs: AST and ALT ≤ 2x ULN **AND** Alk phos ≤ 2x ULN (except when attributable to tumor) **AND** Bilirubin (which one?) ≤ ULN

LVEF ≥ 50% by MUGA or echo (see reviewer comment)

Written informed consent

NED >5 years with the exception of curatively-treated SCC, BCC, or cervical cancer *in situ*

Pregnant or breast-feeding women are excluded

Patients whose life expectancy is ≤ 3 months are excluded

Prior radiation to more than 1/3 hematopoietic sites excluded

NYHA Class II or greater cardiac failure excluded

Uncontrolled systemic infection

Patient non-compliance excluded (not mentioned)

Prior treatment with investigational drug ≤ 30 days excluded

Prior therapy with DOXIL®/CAELYX™

Prior chemotherapy within 28 days for first dose of study drug (42 days for nitrosourea or mitomycin)

Reviewer Comment: Echocardiographically determined LVEF's are considered less accurate and less reproducible. Only two sites will use this method to determine LVEF prior to entry. Data from these two sites should be evaluated carefully.

8.4.3.6 Formulation

DOXIL is supplied in sterile vials, each containing 20mg of doxorubicin hydrochloride at a concentration of 2.0 mg/mL.(v41,p13/23)

8.4.3.7 Experimental Controls

This was a multi-center, randomized, open-label study comparing DOXIL®/CAELYX™ to topotecan in patients failing first-line chemotherapy for ovarian cancer. Patients were to be stratified prospectively for:

(a) platinum sensitivity

(b) bulky disease

8.4.3.8 Dosage Schedule

8.4.3.8.1 DOXIL®/CAELYX™

50 mg/m2 of DOXIL®/CAELYX™ was to be given intravenously over 1 hour every 4 weeks. (v41,p14/24)

8.4.3.8.2 Topotecan

1.5 mg/m2 i.v. over 30 min. daily for 5 consecutive days, starting day1 of a 21-day cycle. (v41,p13/23)

Therapy with either drug is given for up to 1 year in the absence of disease progression. (v41,p13/23)

Guidelines for interval lengthening and/or dose reduction:

Palmar-Plantar Erythrodysesthesia

Grade 1	No previous grade 3-4	No change
	Previous grade 3-4	Delay next cycle 1 week
	Following 2 week delay	Dose reduce 25% and cont. q 4 wk
Grade 2	No previous delay	Delay 1 week
	Following 1 week delay	Delay 1 additional week
	Following 2 week delay	Dose reduce 25% and cont q 4 wk
Grade 3-4	No previous delay	Delay 1 week
	Following 1 week delay	Delay 1 additional week
	Following 2 week delay	Discontinue therapy

Neutropenia or Thrombocytopenia

Grade 2-3	Delay until Grade 1
Grade 4	Delay until Grade 1 and either dose reduce 25% or use cytokine

Hyperbilirubinemia

• 1.2 mg/dL < Bili ≤ 3.0 mg/dL		dose reduce 25%
• > 3.0 mg/dL	Unrelated to DOXIL	dose reduce 50%
	Related to DOXIL	discontinue DOXIL therapy

Stomatitis

Same as dose modifications for PPED

Other Toxicities

Grade 3-4	Delay until Grade 1 + 25% reduce

8.4.3.9 Follow-up Details

Refer to the follow-up schema from the protocol:

Parameter	Pre-Treatment	During Treatment				After Treatment	Follow-up
	≤ 7 days pre-Study	Day 1	Weekly	Every Cycle	Every 2 Cycles	End of Treatment (4 weeks after last dose)	2 mos after end of final cycle (pts with PR or CR)
Informed Consent	X						
QOL Questionnaire		X		X		X	
Medical History	X						
Physical Examination	X			X		X	
Radiological Assessment	X						
MUGA (or echo)	X				X	X	
12-Lead ECG	X						
Hematology	X		X	X		X	
Serum Chemistry	X			X		X	
Serum CA 125	X			X		X	
Urinalysis	X					X	
Pregnancy test	X						
DOXIL®/CAELYX™ Administration		X		X			
Concomitant Medications		X		X		X	
Monitor Adverse Events		X		X		X	
Survival							X

(v41, pvi/9)

Patients underwent pre-therapy assessment within 7-30 days (depending on parameter) of first dose of either drug. Hematologic toxicities were monitored every week. Radiologic imaging was repeated every 8 weeks (2 cycles). Patients who achieve CR or PR are to have a confirmatory scan 4 weeks later. Follow-up for 1 year for survival was intended. LVEF was determined every 2 cycles. Physical examination includes weight, vital signs, and Karnofsky Performance Status.

8.4.3.10 Efficacy Considerations

The primary endpoints were time to progression (TTP) and response rates (RR).

The secondary endpoints were time to response (TTR) duration of response (DOR), survival, health-related quality of life assessment following administration of either drug. (v41,p6/16):

CR was achieved when the following criteria were all met:

Complete disappearance of all measurable AND evaluable disease
No new lesions
No disease-related symptoms
Must persist for 4 weeks

PR was achieved when the following criteria were all met:

Did not achieve a CR
At least 50% decrease in the sum of the products of all bidimensional perpendicular diameters of all measurable lesions
No progression of evaluable disease
No new lesions
Must persist for 4 weeks

Progressive Disease (PD) was achieved when **any** of the following were observed:

50% or greater increase **or** increase **to** 10cm2 (whichever is smaller) in the sum of the products of bidimensionally measured lesions over the smallest sum obtained at best response
Reappearance of any lesions which had disappeared
Clear worsening of any evaluable disease
Failure to return for evaluation due to death or deteriorating condition
Appearance of any new lesion/site

Stable disease: any evidence of disease not meeting the criteria for CR, PR, PD.

For bone disease, increased uptake on the bone scan does not constitute clear worsening of disease. Worsening of existing nonevaluable disease does not constitute progression. (v41,p23/33-24/24)

8.4.3.11 Safety Considerations

All adverse events that occur at any time during the study including post-treatment period were to be recorded in the CRF's. The NCI-CTC was used (Appendix VII) (v41,p18/28).

Attribution to study drug was judged to be either **related, not related,** or **unknown**.

The definition of a serious adverse event includes any experience that:

Is fatal or immediately life-threatening
Is severely or permanently disabling
Requires or prolongs hospitalization
Is a congenital anomaly, cancer, or overdose
Clinically serious

Reviewer comment: By the above criteria, it appears that at least all grade 4 toxicities are included, and suggests that grade 3 toxicities are included as well. However, a specific delineation of what grade 3 vs. grade 4 and hematologic vs. non-hematologic toxicities are included in the term "SAE" is unclear.

8.4.3.12 Statistical Considerations

This trial is an equivalency trial comparing time to progression between DOXIL®/CAELYX™ and topotecan. Topotecan has been shown in a randomized trial to produce a median time to progression of 23 weeks. A difference of < 10% shorter median time to progression or better would be considered a positive result.

Baseline demographic characteristics will be compared between the two treatment groups. Differences between the two will be tested using the Cochran-Mantel-Haenzel (CMH) test and differences in platinum sensitivity and bulkiness of disease will be adjusted for.

Reviewer Summary of Study 30-49

Study 30-49 is a randomized, open-label study of DOXIL®/CAELYX™ versus topotecan in platinum-refractory ovarian cancer. This protocol has been summarized and described. Currently, patients are accruing, and at this interim review of responses, sponsor claims 6 responses out of a total of 44 platinum- and paclitaxel-refractory patients accrued to the DOXIL®/CAELYX™ arm, for a response rate of 13.6% (exact 95% CI 5.2 – 27.4%). This is in comparison to the topotecan arm in which three out of 37 platinum- and paclitaxel-refractory patients were observed yielding a response rate of 8.1% (exact 95% CI 1.7 – 21.9%). A safety review of this study was not included in the submitted application. FDA analysis of efficacy data is continuing, although the responses cited above have not been evaluated by the FDA as of the date of this briefing document.

8.5 Study 22 Independent Radiological Review

An Independent Radiological Review of a Noncomparative, Multicenter Study of DOXIL®/CAELYX™ in the Treatment of Patients with Recurrent or Persistent Epithelial Ovarian Cancer After Initial Therapy with Platinum- and Paclitaxel-Based Regimens

8.5.1 Location of information reviewed in NDA:

Study Item	Volume
Study Report	M52.1

8.5.2 Important Study Dates

Study Dates	13-14 March 1999

This study is based on 25 available CT scans of the 35 patients comprising the ITT population for study 30-22. The investigators were W.P. McGuire, MD, Clinical Professor of Medicine, University of Mississippi, Jackson, Mississippi, and E.K. Fishman, MD, Professor of Radiology and Oncology, Johns Hopkins Medicine, Baltimore, MD. The review was performed in the Department of Radiology at Johns Hopkins University, Baltimore. The scans were reviewed in chronological order and hand measurements were made.

Six responses were confirmed in this independent review (4PR's and 2 CR's) yielding a response rate of 24.0% in the population whose scans were available for review. In terms of ITT analysis, 6/35 patients achieved a response, or 17.1%.

Reviewer comment: The response rate in the reviewed population of 24.0% (exact 95% CI 9.4 – 45.1%) compares poorly with the FDA-determined response rate of 14.8% (exact 95% CI 4.2 – 33.7%) in the platinum- and taxane-refractory population. But, it must be pointed out that these are different populations, and no direct attempt was made to correlate independently determined responses with platinum- and taxane-resistance, by either the sponsor or the FDA.

8.6 Study 47 Independent Radiological Review

An Independent Radiological Review of a Noncomparative, Multicenter Study of DOXIL®/CAELYX™ in the Treatment of Patients with Advanced Epithelial Ovarian Carcinoma

8.6.1 Location of information reviewed in NDA:

Study Item	Volume
Study Report	17

8.6.2 Important Study Dates

Study Date	9 December 1998

This study is based on 59 available CT scans of the 89 patients comprising the ITT population for study 30-47. The investigators were W.P. McGuire, MD, Clinical Professor of Medicine, University of Mississippi, Jackson, Mississippi, and E.K. Fishman, MD, Professor of Radiology and Oncology, Johns Hopkins Medicine, Baltimore, MD. The review was performed in the Department of Radiology at Johns Hopkins University, Baltimore. All patients who had at least a baseline and one follow-up scan were included. The scans were reviewed in chronological order and both hand measurements and Computer Assisted Masked Read were used.

Eight responses were confirmed in this independent review (6PR's and 2 CR's) yielding a response rate of 13.6% in the population whose scans were available for review. In terms of ITT analysis, 8/89 patients achieved a response, or 9.0%.

Reviewer comment: The response rate in the reviewed population of 13.6% (exact 95% CI 6.0 – 25.0%) compares reasonably well with the FDA-determined response rate of 16.7% (exact 95% CI 9.4 – 26.4%) in the platinum- and taxane- refractory population. But, it must be pointed out that these are different populations, and no direct attempt was made to correlate independently determined responses with platinum- and taxane-resistance, by either the sponsor or the FDA.

Integrated Summary of Efficacy and Safety Findings from FDA Review of Clinical Studies Submitted with sNDA 50-718

The sNDA 50-718 SE-006 for DOXIL in platinum- and paclitaxel- resistant ovarian cancer is comprised of six studies: four clinical trials and two independent radiological reviews. The four clinical studies are of three different designs: 30-22 is a two-center, phase II single-arm, open-label design with DOXIL administered at 50 mg/m2 every three weeks times three; study 30-47 and study 30-47E are both multi-center single-arm open-label studies with DOXIL administered at 50 mg/m2 every four weeks (30-47 was done in the US, while 30-47E was done in Europe), and clinical study 30-49 is a phase III prospective open-label randomized comparison of topotecan 1.5mg/m2 daily times five every three weeks versus DOXIL 50 mg/m2 once every four weeks. Data from study 30-49 are from an interim analysis of this ongoing study. Two independent radiological reviews, study 30-22IR and study 30-47IR are included with this submission, corresponding to study 30-22 and study 30-47, respectively.

Efficacy results from each of the clinical studies are summarized in the table entitled "Overview of Clinical Studies with Respect to Primary Endpoint" found at the begininning of this document. In study 30-22, of the 35 patients enrolled, 27 were found to meet platinum- and taxane- resistance criteria (either progression or relapse within 6 months of completing a platinum- and paclitaxel- containing regimen). Of these 27 platinum- and paclitaxel-resistant patients, 6 were found to have confirmed responses, giving a response rate of 22.2% (95%CI 8.6 – 42.3%). Independent radiological review of 25 patients' scans revealed six responses for a response rate of 24% (95%CI 9.4 – 45.1%).

Study 30-47 was analyzed similarly. Of the 89 enrolled patients, 82 met the criteria for platinum- and paclitaxel-resistance. Within this subset of 82 patients, fourteen confirmed responders were noted for a response rate of 17.1% (95%CI 9.7 – 27.0%). Independent radiological review of this same study was based on 59 patients' scans of the 89 patients total in the study population. Eight responses noted in the 59 scans reviewed yielding a response rate of 13.6% (95%CI 6.0 – 25.0%) for this radiological review.

Study 30-47E utilized the same design as study 30-47, but was conducted in Europe. Zero responses were noted in the 36 platinum- and paclitaxel-resistant patients within the 52 patients accrued at the time of data cutoff of this ongoing study. The 95% CI for this study's response rate is 0.0 – 9.7%.

Study 30-49 is the only randomized clinical trial included in this application. Like study 30-47E, this study is still ongoing. At the time of data cutoff, 44 platinum- and paclitaxel-resistant patients had been accrued to the DOXIL arm, and 37 such patients to the topotecan arm. Responses were observed in six and three patients respectively, for a response rate in the DOXIL arm of 13.6 % (95% CI 5.2 – 27.4%) and 8.1% (1.7 – 21.9%) in the topotecan arm.

Combining the phase II studies 30-22, 30-47 and 30-47E, one calculates a platinum- and paclitaxel-resistant subpopulation of 145, in which 20 responders were observed, yielding an overall response rate of 13.8% (95% CI 8.1 – 19.8%).

There appears to be wide variability of response rates between clinical studies, ranging from 0% to 22.2%, and between the two independent radiological reviews ranging from 13.6% to 24%. All reported response rates have wide 95% confidence intervals, reflecting the relatively small numerators and denominators in each of the studies.

Turning to a summary of safety data, the applicant has provided two concise tables at the end of the study reports for studies 30-22 and 30-47. Many of the differences in toxicity between the two trials are explained by the difference in schedules. In one study, 30-22, DOXIL was administered every three weeks times three, whereas in study 30-47, DOXIL was administered every four weeks times six.

The most common adverse event noted in both study 30-22 and 30-47 was **palmar-plantar erythrodysesthesia**. It was present in approximately 86% of the 35 patients accrued to study 30-22 versus approximately 42% in study 30-47. Similarly, cutaneous toxicities were noted in study 30-22 than in study 30-47, namely **rash** (46% vs. 28%), **vesiculobullous rash** (11.4% vs. <10%), **exfoliative dermatitis** (20% vs. <10%). Toxicity to the mucous membranes was also common. Comparing the incidences between studies 30-22 and 30-47, this included **stomatitis** (57% vs. 22%), **"mucous membrane disorder"** [COSTART preferred term used for **mucositis**] (21.3% vs. 11.4%), and **pharyngitis** (14.3% vs. <10%). **Asthenia** was also more frequent in study 30-22 than in study 30-47. In study 30-22 there was a reported incidence of 69% versus 42 % in study 30-47. Hematologic toxicity was also greater in study 30-22 including **leukopenia** (51% vs. 39%) and **neutropenia** (51% vs. 37%), although **anemia** appeared to be similar in incidence (37% vs. 39%) as did **thrombocytopenia** (<10% in each study). Lastly, gastrointestinal toxicity appears to be more frequent under three week administration versus the four week administration. The incidence was greater in study 30-22 than in study 30-47 for **nausea** (54% vs. 38%), **vomiting** (49% vs. 19%), **anorexia** (31% vs. 14%) and **diarrhea** (34% vs. 12%).

In summary, most adverse events associated with DOXIL administration, (cutaneous, mucosal, hematologic, and gastrointestinal toxicities) were increased in incidence with a three-week as opposed to four-week administration schedule.

Recommended Changes to the Proposed Labeling

Refer to the applicant's proposed labeling. The following are significant changes recommended by the review team: (1) addition of efficaty data from the individual phase II studies rather than just including pooled efficacy; (2) addition of a warning about a the leukemogenic potential of anthracyclines; (3) addition of a safety section specific to the particular dose and administration schedule studied for the ovarian cancer population (50 mg/m2 every 4 weeks versus the KS dose of 20 mg/m2 every 3 weeks); (4) (b) (4) [redacted].

Minor changes to the label are still being discussed between the applicant and the Agency at the time of this summary, 24 June 1999.

Advisory Committee Presentation and Committee Vote

The Agency's review of sNDA 50-718 was presented at the Oncology Drug Advisory Committee meeting during the morning session of 8 June 1999

There were two questions to the committee:

1. Do the data on objective response indicate that DOXIL is "reasonably likely" to be associated with clinical benefit in this population?

   YES – 9 NO – 2

2. Considering the efficacy discussed in question #1 and the toxicity described above, do you recommend that DOXIL, 50 mg/m2 administered intravenously every 4 weeks, be granted accelerated approval for the treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regiments? (Refractory is defined as a patient having progressive disease while on treatment, or within 6 months of completing treatment.)

   YES – 9 NO – 2

Complete responses to second line therapy are rare, and with an overall 13.8% response rate, it is unlikely that there will be any impact on survival data. Symptom control, or improvement in symptoms or in quality of life, would represent an advance in second line therapy for this indication, and the Committee recommends that further clinical trials to elucidate these endpoints be stipulated in any approval letter. Data from the primary setting is also needed, where it is possible that a survival advanctage could be determined.

The committee vote was 9-2 in favor of approving DOXIL for its proposed indication: *"The treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory is defined as a patient having progressive disease while on treatment or within 6 months of completing treatment."* The vote was followed by a discussion about important design features to be incorporated into the post-marketing study(-ies) to which the applicant is obligated for full approval. The review of the draft proposed labeling is pending.

DRAFT

Reviewer recommendation: The data I have reviewed from this application lead me to the following conclusions. Efficacy claims are based on response rate, which is a relatively poor endpoint by which to evaluate true clinical benefit to patients. According to Dr. Richard Simon, a member of the committee, and who has published on this subject, there is a poor relationship between response rate and overall survival in this population (multiply pre-treated ovarian cancer). Thus, with respect to response rate, clinical benefit does not appear to be predicted for. Alternatively, in anecdotal cases large tumor bulk was very responsive, and significantly decreased in size following one to a few cycles of DOXIL. In addition, the toxicity arising from the dose and administration schedule studied (50 mg/m2 over 1 hour every four weeks) was non-trivial (both in terms of spectrum and magnitude). The majority of patients required dose delay, dose reduction, or both.

In summary, my enthusiasm for DOXIL in this setting is largely attenuated by the limited response rate that may not translate into clinical benefit and the added burden of predictable toxicity. Were it not for the anecdotal instances of clear clinical benefit on a case-by-case basis, I do not believe DOXIL would occupy any position in the antineoplastic armamentarium.

Gregory K. Frykman, MD
Reviewing Fellow
Division of Oncology Drug Products, HFD-150
24 June, 1999

I concur with Dr Frykman's review of the data.
I recommend accelerated approval be granted
for the proposed indications. See Team Leader memo.

Grace Williams MD 6/25/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-718/S-006

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-150 DODP	50-718

3. NAME AND ADDRESS OF APPLICANT *(City and State)*
Sequus Pharmaceuticals, Inc.
960 Hamilton Court
Menlo Park, CA 94025

4. AF NUMBER

5. SUPPLEMENT (S) NUMBER(S) DATES(S)

6. NAME OF DRUG	7. NONPROPRIETARY NAME	SE1 006	12-21-1998
DOXIL	Doxorubicin HCl liposome injection		

8. SUPPLEMENT PROVIDES FOR: a new indication of Doxil in the treatment of patients with metastatic carcinoma of ovary.

9. AMENDMENTS DATES

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
Antineoplastic	RX √ OTC ____	

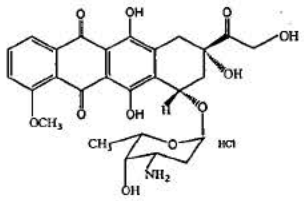
13. DOSAGE FORM(S)	14. POTENCY
IV	20 mg/vial (2mg/ml)

15. CHEMICAL NAME AND STRUCTURE

(8*S-cis*)-10-[(3-Amino-2,3,6-trideoxy-a-L-lyxo hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroacetyl)-1-methoxy-5,12-naphthacenedione

$C_{27}H_{29}NO_{11}.HCl$

MW = 579.99



16. RECORDS AND REPORTS

CURRENT YES √ NO ___

REVIEWED YES √ NO ___

17. COMMENTS

The applicant is seeking a new indication for the marketing drug Doxil to treat the patients with metastatic carcinoma of the ovary. There is no chemistry manufacturing and controls change for this new indication. The package insert of Doxil was submitted. (b) (4) [redacted]

18. CONCLUSIONS AND RECOMMENDATIONS

Approval is recommended from CMC point of view. (b) (4) [redacted]

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Chengyi Liang, Ph.D.	Chengyi Liang	4-27-1999

DISTRIBUTION	ORIGINAL JACKET	DIVISION FILE	Reviewer: C.Y. Liang HFD-150	CSO: A. Dunson HFD-150	Chemistry Team Leader: L.Zhou

L. Zhou 5/17/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-718/S-006

STATISTICAL REVIEW(S)

A. DUNSON

STATISTICAL REVIEW AND EVALUATION

MAY 17 1999

Supplement to NDA#:	50-718 / S-006
Applicant:	SEQUUS Pharmaceuticals, Inc. Menlo Park, California
Name of Drug:	DOXIL® (doxorubicin HCl liposomal injection)
Indication:	Treatment of patients with metastatic ovarian cancer who are refractory to both paclitaxel- and platinum-based chemotherapy regimens [redacted] (b) (4) Refractory is defined as a patient having progressive disease while on treatment, or within six months of completing treatment.
Documents Reviewed:	Volumes 1, 2, 3, 6, 7, 10, 11, 16, 18, and 19 and ACCESS DB files
Medical Officers:	Greg Frykman, M.D. Grant Williams, M.D.

I BACKGROUND:

The sponsor has submitted two pivotal uncontrolled Phase II trials in refractory patients (#30-22 and #30-47) conducted in the U.S. and #30-47E conducted in Europe. #30-22 has been completed while #30-47 and #30-47E are ongoing. Also submitted as supporting evidence are: (1) a preliminary interim response data analysis (done before the protocol specified interim analysis at FDA's request) on a randomized Phase III trial (#30-49) of Doxil vs. Topotecan in patients with epithelial ovarian carcinoma following failure of first line chemotherapy with a platinum-based regimen and (2) an independent review of radiological images used to evaluate tumor response from #30-47. The primary analysis is based on pooling data from #30-22 (completed, N=35) and #30-47 (ongoing, N=89 of 120). The primary efficacy endpoint, tumor response rate, is estimated with associated confidence interval (C.I.) for the pooled group of 110 double refractory (to taxol and platinum) patients in these studies; 33 of these patients were also refractory to topotecan. A secondary analysis is provided on these two U.S. studies pooled with the European Phase II trial. The primary intent-to-treat analysis group is defined as enrolled patients who have received any amount of study drug. Evaluable patients analysis (those who

received at least two cycles of study drug and had at least one response evaluation) is also provided. Secondary endpoints are time to response, duration of response, and time to progression (TTP). #30-47 also collected data on QOL measures.

II SUMMARY OF EFFICACY RESULTS:

Study #30-22: This study is entitled "Pharmacokinetics and Response to DOXIL (STEALTH Liposomal Doxorubicin HCl) in Patients with Recurrent or Persistent Ovarian Cancer After Initial Therapy with Platinum and Paclitaxel-based Regimens." It is an open-label, noncomparative, multicenter (two centers) trial of 50 mg/m^2 of DOXIL every three weeks. The study group comprised patients with histologically proven or persistent epithelial ovarian carcinoma who were platinum and paclitaxel failures and had clinically measurable disease. A total of 35 female patients (29 evaluable) were enrolled. All 35 patients had persistent or clinically recurrent epithelial ovarian cancer and had received platinum- and paclitaxel-based regimens without achieving a pathological CR. Study objectives were to "determine the pharmacokinetics of DOXIL in patients with epithelial ovarian cancer and to define the response to DOXIL in patients with epithelial ovarian cancer who have failed treatment with both platinum-based and paclitaxel-based treatment regimens. In addition, the safety and tolerance of DOXIL were to be summarized." The primary efficacy endpoint was durable (confirmed) response defined as a complete (CR) or partial response (PR) that lasted at least 21 days. Secondary efficacy endpoints include time to response and duration of response (measured from first observation of a response). Efficacy evaluations were carried out on two patient populations, viz., intent-to-treat group comprising all patients enrolled and the evaluable patients group comprising those patients who received at least three cycles of study drug.

Sponsor's Reported Efficacy Results: Median patient age was 62.5 years (range: 46-78) and the majority were white (88.6%). 28 were refractory to both platinum and paclitaxel. One patient completed the protocol, 27 terminated due to progressive disease (PD), and 7 terminated due to adverse events, two of which were considered possibly drug related. 61.3% of the DOXIL doses administered were delayed, reduced, or interrupted. Adverse events (AE's)/toxicity accounted for 41.9% of the dose modifications. The most common AE leading to dose modification was palmar-plantar erythrodyesthesia (PPE).

Efficacy Findings: The sponsor's objective response rate findings for the ITT group revealed 7/35 or 20%. 7/29 (24.1%) evaluable patients responded (95% CI: 9%-40%) comprising one CR and six PR's. Median time to response was 23.9 weeks (range: 12.6-29.0 weeks). Median response duration was 61 weeks (range: 19.0-67.0 weeks). For evaluable patients median time to progression (TTP) was 27.7 weeks (range: 7.7-112.7 weeks). For the Double-Refractory Subpopulation: 6/28 (21.4%) responded (95% CI: 6%-37%), 1 CR and 5 PR's. Median time to response was 21.6 weeks (range: 12.6-29.0 weeks). Median response duration was 61 weeks (range: 19.0-67.0 weeks). Median TTP in this group was 22.9 weeks (range: 2.1-112.7 weeks).

Safety Findings: The most commonly occurring AE's were: PPE (54.3%), asthenia (68.6%), stomatitis (57.1%), nausea (54.3%), leukopenia (51.4%), and neutropenia (51.4%). Seven patients withdrew from the study due to severe AE's; 2/7 withdrew due to events considered

possibly related to study drug. There were no treatment-related deaths.

Study #30-47: This study is entitled "A Noncomparative, Multicenter Study of DOXIL*/CAELYX* in the Treatment of Patients with Advanced Epithelial Ovarian Carcinoma." It is an open-label, noncomparative, multicenter (18 centers) study of DOXIL for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma following failure of at least two but no more than three prior cytotoxic chemotherapy regimens. The design was as follows. 50 mg/m^2 of DOXIL was administered by intravenous infusion every 4 weeks (1 cycle); treatment was to continue for 6 cycles or until disease progression or dose-limiting toxicity. The first stage was to enroll 33 evaluable patients. If there were at least four responders, enrollment was continued until 20 additional evaluable patients had been entered. An interim analysis was performed after the first 34 evaluable patients were enrolled. There were 7/34 responders and enrollment continued into stage II. Protocol amendment 2 restricted enrollment to include only triple-refractory patients. The same two-stage design was applied to the triple-refractory cohort. There were 5 responders in stage I, and enrollment continued into the second stage. For purposes of the NDA report 90 patients enrolled not later than 2/2/98 were included. Study objectives were "to describe response rate, time to response, duration of response, time to progression , survival, and safety of DOXIL/CAELYX in patients with locally advanced or metastatic, epithelial ovarian carcinoma who had failed at least 2 but not more than 3 prior chemotherapy regimens. Pilot data also were obtained about the use of the Health-Related Quality of Life (HQL) questionnaires." Primary efficacy analyses were done for both the intent-to-treat (ITT) and evaluable populations. In addition, an analysis was performed on those patients who were double-refractory, i.e., having progressed while being treated with a platinum- or taxane-based regimen.

Sponsor's Reported Efficacy Results: Median patient age was 61 years (range: 34-85). Baseline median Karnofsky performance status was 90. Eighty-two of the 90 patients enrolled were double-refractory. One patient received no DOXIL.

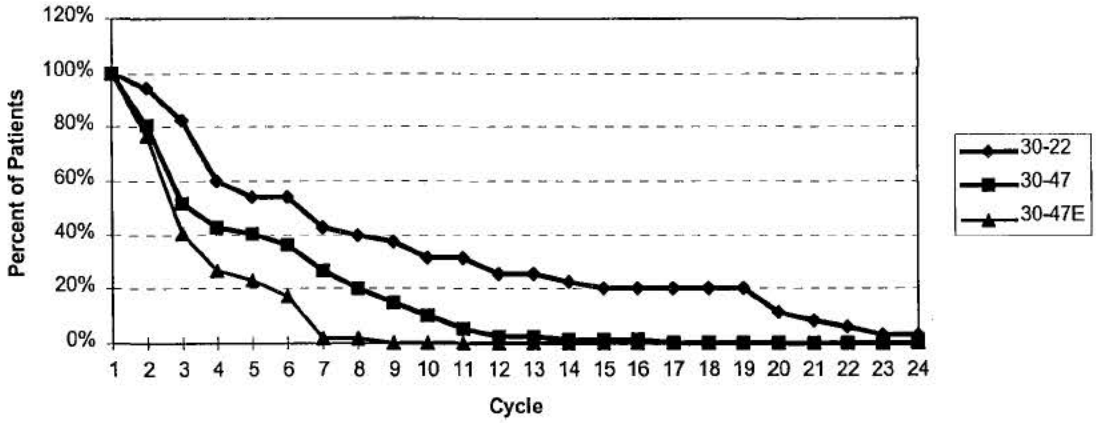
Efficacy Findings: For the 89 ITT patients the objective response rate was 16.9%; median TTP was 135 days. For the evaluable patients cohort the objective response rate was 15/63 (23.8%). The 15 responders (1 CR and 14 PR's) had a median time to response of 106 days (range: 23 to 230 days) and a median duration of response of 169 days (range: 32+ to 338 days). For evaluable patients the median TTP was 198 days (range: 49 to 602 days). The subgroup of 59 evaluable double-refractory patients included the 15 responders, yielding an objective response rate of 25.4%. The subgroup of 82 ITT double-refractory patients had a response rate of 18.3%; their median TTP was 119 days (range: 5 to 501 days).

Safety Findings: Of the 89 patients who received DOXIL, 7 (7.9%) terminated due to death. Each of these was attributable to progressive disease (PD) and none were considered related to study drug. Fifteen patients (16.9%) withdrew due to adverse events (AE's). For 10 of these the events were considered study drug-related: grade 3 PPE (3 patients), grade 3 asthenia (2 patients), and 1 patient each for grade 4 neutropenia, grade 4 stomatitis, grade 3 cardiotoxicity, severe edema of feet and hands, and grade 1 decline in LVEF. Eighty-four patients (94.4%) had AE's deemed possibly or probably related to study drug. The sponsor states that PPE is the dose-limiting toxicity which can be successfully managed by increasing the dosing interval

and/or decreasing the dose.

Quality of Life Findings: For the 50 patients who were enrolled after the first protocol amendment, 34 completed the pretreatment HQL questionnaire and had at least one post-baseline assessment. Fifteen questions bearing on potential chemotherapy-related effects were administered. Sample sizes and responses by cycle are presented in SPONSOR's TABLE 1 in the REVIEW APPENDIX. Given the high attrition rates encountered and lack of a control arm, no firm conclusions can be drawn. As the sponsor states: *"It is apparent that the number of patients declines with increasing cycle number. The withdrawal of patients due to progressive disease or other reasons may leave proportionally more patients in the study who are able to tolerate the treatment and therefore could experience an improved quality of life. This makes it difficult to determine if improvements in QOL scores are due to treatment or due to selective elimination of patients with worse quality of life."* The following plot, provided by the sponsor, presents attrition patterns for the three uncontrolled studies in the integrated summary. For #30-47 it can be seen that approximately 50% of the patients had dropped out by cycle 3.

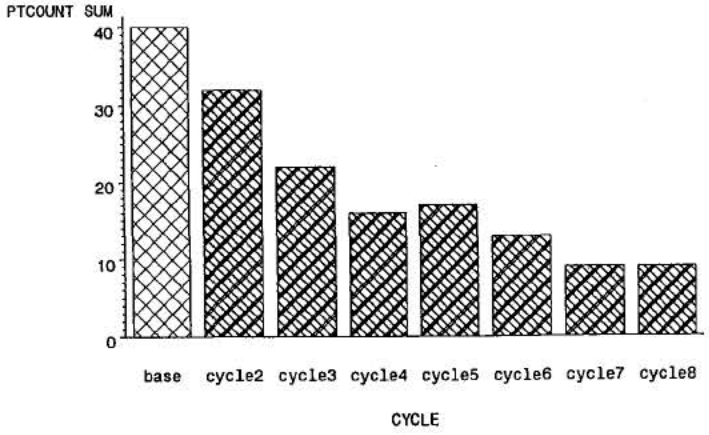
Percent of Patients By Cycle By Study



More specifically, for QOL analysis, the following two reviewer's plots present attrition patterns for the EORTC QLQ-C30 assessments and chemotherapy-related questions indicating the same problem.

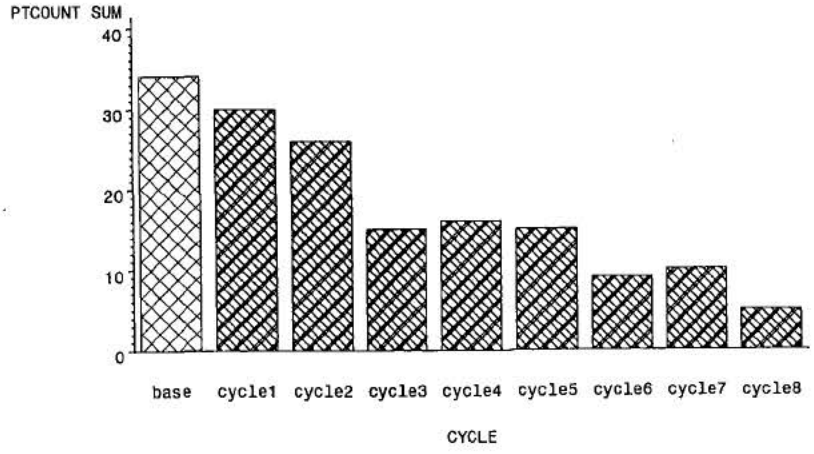
REVIEWER's PLOT 1

MISSING DATA PATTERN / QOL QUESTIONS



REVIEWER's PLOT 2

MISSING DATA PATTERN / CHEMORX QUESTIONS



Study #30-47E: The design of this study was similar to #30-47 but it was conducted in Europe.

An interim analysis was conducted on 52 patients, including 36 patients with disease refractory to platinum and taxane regimens. Median patient age was 53.5 years and the majority were white (94%). 57.7% had serous papillary histologic tumor type.

Sponsor's Reported Efficacy Results: Within the group of 36 patients who were refractory to both platinum and paclitaxel regimens, none had a confirmed response to DOXIL.

Study #30-49: This study is a comparative, prospectively randomized trial stratified for platinum sensitivity and bulk disease in patients with epithelial ovarian carcinoma following failure of first-line platinum-based chemotherapy. The comparator arm is Topotecan. At the request of FDA an interim analysis of preliminary efficacy data was conducted. A total of 239 patients were included; 119 treated with DOXIL and 120 treated with Topotecan. The treatment groups were well matched in terms of sensitivity to prior platinum therapy and bulkiness of disease. Fourteen (11.8%) DOXIL-treated patients had confirmed objective responses (4 CR's and 10 PR's); Fourteen (11.7%) Topotecan-treated patients had confirmed objective responses (3 CR's and 11 PR's). Response rates were similar when considering sensitivity to prior platinum therapy and bulkiness of disease. Of patients refractory to prior platinum therapy 3/56 (5.4%) DOXIL and 1/58 (1.7%) Topotecan patients had confirmed responses.

Integrated (Pooled) Efficacy Summary: The following sponsor's tables present the results of their pooled summary for objective response rate and secondary efficacy endpoints.

	Refractory Patients		All Patients	
Study	Evaluable	ITT	Evaluable	ITT
30-22	25	28	29	35
30-47	59	82	63	89
Subtotal US Studies	84	110	92	124
30-47E	22	36	36	52
Total All Studies	106	146	128	176

Summary of Integrated Response Rate
US Studies Refractory Patients ITT Population

Number of Patients	110
Responders	
Complete	2 (1.8%)
Partial	19 (17.3%)
Responders	21 (19.1%)
95% Confidence Interval	11.7% to 26.4%
Non Responders	
Unconfirmed CR/PR	3 (2.7%)
Stable Disease	38 (34.5%)
Progressive Disease	30 (27.3%)
No Data Available	18 (16.4%)

Source: Table 25

Secondary Efficacy Parameters
ITT Analysis of US Studies

Time to Response (days)	
N	21
Median	123
Range	23 to 230
Duration of Response (days)	
N	21
Median	276
Range	32+ to 469
Time to Progression (days)	
N	110
Median	131
Range	5 to 789+

Source: Table 25

Summary of Integrated Response Rate
All Studies Refractory Patients ITT Population

Number of Patients	146
Responders	
Complete	2 (1.4%)
Partial	19 (13.0%)
Responders	21 (14.4%)
95% Confidence Interval	8.7% to 20.1%
Non Responders	
Unconfirmed CR/PR	6 (4.1%)
Stable Disease	47 (32.2%)
Progressive Disease	44 (30.1%)
No Data Available	28 (19.2%)

Source: Table 33

Secondary Efficacy Parameters
ITT Analysis of All Studies

Time to Response (days)	
N	21
Median	123
Range	23 to 230
Duration of Response (days)	
N	21
Median	276
Range	32+ to 469
Time to Progression (days)	
N	146
Median	111
Range	5 to 789+

Source: Table 33

III RELEVANT STATISTICAL ISSUES:

(1) The primary analysis is based on pooling data from two studies, one of which is ongoing. Estimates are calculated based on approximately 75% of the data from #30-47 and complete data from #30-22. A potential concern is that response rate estimates may be inflated. However, given the size of the response rate estimate, maturity of the data and the sample size, it is unlikely that an adjustment for sequential estimation would change the associated C.I. in a substantial way.

(2) The unplanned interim analysis (IA) on the Phase III response data doesn't require adjustment since the intent was not potential early stopping to claim benefit, but rather to provide FDA with supportive data comparing DOXIL response rates with other agents. The intent is really descriptive in nature. The planned IA will be carried out when the first 200 enrolled patients have been followed for six months or until disease progression (PD). The FDA requested unplanned analysis was conducted on the same patient population described in the planned IA, but with a much shorter follow-up (8-week minimum). Thus, response rate estimates are probably deflated.

(3) The quality of life (QOL) analysis provided for #30-47 is problematic due to high attrition rates and lack of a control arm. For both the group of fifteen questions on chemotherapy-related effects and the EORTC QLQ-C30 instrument questionnaire, half of the patients with pretreatment assessments had dropped out by the third treatment cycle. For the QOL instrument functioning scales and global health status the sponsor's approach was to compare the last recorded score to baseline. This strategy can lead to biased results depending upon the amount and pattern of missing data and it ignores the temporal aspect of these inherently longitudinal measures. Given the attrition pattern and lack of a control arm, only descriptive displays are meaningful and no firm conclusions can be drawn. This is a secondary endpoint and the sponsor is making no improved QOL claims in this uncontrolled setting. The sponsor stated that the goal of these assessments was to pilot the use of these instruments in order to gain experience with them.

Conclusion: The ultimate approval decision must be a clinical one. The question is does the benefit claimed, in terms of tumor response rate, outweigh the Doxil associated toxicities in this highly refractory group of patients.

Clare Gnecco

Clare Gnecco, Ph.D.
Mathematical Statistician

Concur: Dr. Chen chen Concur, 5/12/99

Dr. Chi Chi

cc:
sNDA #50-718/S-006
HFD-150/Division File
HFD-150/Dr. Frykman
HFD-150/Dr. Williams
HFD-150/Mr. Dunson
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Chen
HFD-710/Dr. Gnecco
HFD-710/Chron

CGNECCO/04-29-99/MS-WORD7/DOXS006.DOC

This review consists of 10 pages of text.

REVIEWER'S APPENDIX 1

Sponsor's Table of Summary Results for Questions
On Chemotherapy-Related Effects

	A/B (ratio)					
No.	BL, n=34	Cycle 1, n=30	Cycle 2, n=26	Cycle 4, n=16	Cycle 6, n=9	EOT, n=34
36	1/32 (0.03)	2/28 (0.07)	1/24 (0.04)	1/14 (0.07)	0/9 (0)	0/34 (0)
37	1/32 (0.03)	0/30 (0)	3/22 (0.14)	0/15 (0)	0/9 (0)	0/34 (0)
38	0/33 (0)	0/30 (0)	1/25 (0.04)	0/14 (0)	0/9 (0)	0/34 (0)
39	0/33 (0)	0/30 (0)	0/25 (0)	0/15 (0)	0/9 (0)	0/33 (0)
40	8/25 (0.32)	4/26 (0.15)	1/25 (0.04)	2/13 (0.15)	1/8 (0.13)	3/30 (0.10)
41	0/33 (0)	1/29 (0.03)	6/20 (0.30)	4/11 (0.36)	1/8 (0.13)	5/27 (0.19)
42	5/28 (0.18)	5/24 (0.21)	3/23 (0.13)	2/14 (0.14)	1/8 (0.13)	9/23 (0.39)
43	1/32 (0.03)	1/29 (0.03)	2/24 (0.08)	1/15 (0.07)	2/7 (0.29)	2/32 (0.06)
44	2/30 (0.07)	3/27 (0.11)	1/25 (0.04)	2/14 (0.14)	2/7 (0.29)	4/30 (0.13)
45	0/33 (0)	2/28 (0.07)	4/22 (0.18)	5/11 (0.45)	3/6 (0.50)	7/27 (0.26)
46	2/31 (0.06)	1/28 (0.04)	3/22 (0.14)	4/12 (0.33)	2/7 (0.29)	6/27 (0.22)
47	2/31 (0.06)	2/28 (0.07)	1/25 (0.04)	2/14 (0.14)	0/9 (0)	2/31 (0.06)
48	3/30 (0.10)	5/25 (0.20)	1/25 (0.04)	2/14 (0.14)	1/8 (0.13)	5/29 (0.17)
49	0/33 (0)	1/29 (0.03)	4/22 (0.18)	3/13 (0.23)	3/6 (0.50)	3/30 (0.10)
50	1/32 (0.03)	0/30 (0)	0/26 (0)	1/15 (0.07)	2/7 (0.29)	1/32 (0.03)

The above Table summarizes the number of patients with answers of *very much* or *quite a bit* (A) over those with answers of *a little* or *not at all* (B) at baseline (BL), cycles 1, 2, 4, 6, and end of treatment (EOT). Note that where $A + B \neq n$, the difference (≤ 2) is due to missing data.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-718/S-006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Recommendations to the Oncology Clinical Division on the review of an sNDA

NDA: 50-718/006
Drug: Doxil (doxorubicin HCl liposome injection)

Clinical Division: Oncology
Sponsor: SEQUUS Pharmaceuticals, Inc.

Reviewer: Lydia V. Kieffer, Pharm.D.
Team Leader: Atiqur Rahman, Ph.D.

Doxil is currently indicated for the treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy. The recommended dose of 20 mg/m^2 is administered intravenously over 30 minutes, once every 3 weeks, for as long as patients respond satisfactorily and tolerate treatment. The supplemental NDA submitted seeks approval in the "treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regimen [redacted (b) (4)]".

The sponsor conducted two studies in order to characterize the pharmacokinetics of Doxil. One of the studies was a Phase II clinical trial (study 30-22) conducted in the targeted population for the purpose of characterizing the pharmacokinetics of Doxil in ovarian cancer patients. The second study submitted is a population pharmacokinetic analysis study involving pharmacokinetic data from 120 patients (81 males, 39 females) from 10 different clinical trials. The Phase II trial in the ovarian population (study 30-22) was one of the 10 trials utilized for the population pharmacokinetic analysis. Plasma samples were analyzed using a validated HPLC method with fluorescence detection that did not distinguish liposome-encapsulated doxorubicin from nonliposomal doxorubicin.

Issues:

1. **Case report on a patient with elevated bilirubin levels:** [redacted (b) (4)] The results of the population pharmacokinetic study can not be verified due to the submission of the incorrect data input file.

- Doxil pharmacokinetics in a patient with high bilirubin levels (Appendix D, Vol. 4): The patient described (AIDS-KS) received a 1 time 5 mg/m2 dose during cycle 1 followed by a dose of 20 mg/m2 for the second cycle. The assumption that the information provided from this case report can be extrapolated to a dose 1.5 to 5 times the administered dose is based on linear kinetics of Doxil up to 20 mg/m2 dose. The sponsor has stated that the

pharmacokinetics of Doxil at higher doses (40-50 mg/m2) than the KS indication have demonstrated nonlinearity. Predicting pharmacokinetics of 1.5 to 2.5 the dose administered in a possibly compromised liver as demonstrated by elevated bilirubin levels should not be done because of the potential nonlinear kinetics. [redacted] (b) (4)

2. **Pharmacokinetic Study in the Targeted Population:** Due to the submission of the wrong input file in the population analysis, we are unable to identify the corresponding data for the targeted population for verification purposes. The sponsor submitted a summary of the targeted population's pharmacokinetic parameters; but no means of verifying the data. However, the sponsor is claiming that the population pharmacokinetic parameters obtained from the analysis are the same as the pharmacokinetic parameters from study 30-22. Clarification by the sponsor will be required.

- The protocol states that patients with ascites or a pleural effusions would undergo an additional blood sample collection (minimum volume 5 mL) 1 hour post infusion. At the advisory committee meeting on June 8th, 1999, the sponsor stated that 5 patients had ascites during the clinical trials. Please provide the pharmacokinetic data for those 5 patients and/or a means of identifying those patients in the electronic data sets for analysis purposes if available.
- During the advisory committee meeting, much deliberation took place regarding the appropriate phase 3 trial to be conducted for the full approval of Doxil in the targeted population. Characterizing the pharmacokinetics in the targeted population with the correct dose and regimen should be part of the objectives of the trial. As mentioned at the advisory committee meeting, patients with ascites and malignant pleural effusions may be encountered in the community at a greater frequency than was observed during the clinical trials. As a result, the pharmacokinetics in this subpopulation should be investigated due to the safety concerns expressed at the advisory committee meeting. It may very well be that the pharmacokinetics of Doxil are quite different in patients with ascites or malignant pleural effusions.
- Since the previous indication's pharmacokinetics was conducted in a predominantly male population, a pharmacokinetic analysis will also resolve any gender related issues associated with Doxil in females in the proposed indication.
- The previous indication called for a Doxil dose that displays linear pharmacokinetics (20 mg/m2). The new dose for the proposed indication (50 mg/m2) displays nonlinear pharmacokinetics. Moreover, the submitted pharmacokinetic data for the new indication was conducted with a different regimen than what is being proposed (conducted with an every 3 week regimen versus an every 4 week regimen). Therefore, providing altered pharmacokinetics of Doxil at the recommended dose (50 mg/m2) in the package insert would be of benefit.

3. **Population Pharmacokinetic Study:** The incorrect data input file was submitted. As a result, the population pharmacokinetic analysis was unverifiable.

- The data input file with the study site/tumor type as a covariate studied needs to be submitted.
- The files submitted do not reflect bilirubin being investigated as a possible covariate, yet the sponsor describes the results of such an analysis being conducted. This will required further clarification.
- Study 30-22 (pharmacokinetic study in the targeted population) should be compared to the population pharmacokinetic analysis study performed to investigate whether the pharmacokinetics of Doxil behaves the same or differently across cancer populations. The final model should be appropriately presented with supportive raw data and input files. The data from study 30-22 should be submitted to the Agency in a way that will allow for verification of the raw data.
- The sponsor states that the approximate 2-fold difference observed in their summary of simulated concentrations due to tumor type effect in the two extreme cases (AIDS-related Kaposi's sarcoma and breast cancer patients) will probably not result in any serious toxicity that would require changes in dosing schemes. The simulations seem to have been carried out to 1.5 cycles, whereas the patients with ovarian cancer are expected to be treated for at least four cycles. Therefore the simulation appears to be inadequate for predicting any long term pharmackinetic changes of Doxil due to tumor types. Simulation data will have to be submitted in order for the Agency to assess the appropriateness of the simulations, verification of the simulations, and their applicability in this setting.

4. **Assay Methodology:** The sponsor can not detect doxorubicinol in this submission utilizing the same assay employed in the original NDA with Doxil doses ranging from 50 to 60 mg/m^2, yet the KS package insert describes doxorubicinol being detected at Doxil doses of 10 to 20 mg/m^2. As a result, the sponsor will be required to address the disparity observed between the NDA and sNDA submissions.

5. **Proposed Labeling:** (b) (4)

Recommendation to the Clinical Division: Based on the above issues the supplemental application is deficient from the Clinical Pharmacology and Biopharmaceutics perspective. The sponsor should submit the clinical pharmacokinetic data as a Phase IV commitment for Agency review and for incorporation of adequate Clinical Pharmacology information in the package insert.

Lydia Velazquez Kieffer

Lydia Velazquez Kieffer, Pharm.D.
Reviewer 6-9-99
Division of Pharmaceutical Evaluation I

A.M. Atiqur Rahman 6/18/99

Atiqur Rahman, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation I

cc: IND 36,778
NDA 50,718
HFD-150/ Division File
HFD-150/ ADunson, GWilliams, GFrykman
HFD-150/DYLeeHam, PAndrews
HFD-850/ LLesko
HFD-860/ MMehta, ARahman, LVelazquezKieffer
CDR BMurphy

Clinical Pharmacology and Biopharmaceutics sNDA Review

NDA 50-718/SE1-006 **Submission Date:** December 21, 1998

Drug Name:	Doxil ® (doxorubicin HCl liposome injection)
Formulation:	20 mg sterile vial, 2 mg/mL concentration
Sponsor:	SEQUUS Pharmaceuticals, Inc. 960 Hamilton Court Menlo Park, Ca. 94025
Reviewer:	Lydia Velazquez Kieffer, Pharm.D.

Synopsis: Doxil consist of the cytotoxic anthracycline antibiotic doxorubicin encapsulated in long circulating microscopic liposomes that are formulated with surface-bound methoxypolyethylene glycol (MPEG) . These MPEGs protect the liposomes from detection from the immune system and increase blood circulating time. Doxil is currently indicated for the treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy. The recommended dose of 20 mg/m^2 is administered intravenously over 30 minutes, once every 3 weeks, for as long as patients respond satisfactorily and tolerate treatment. The supplemental NDA submitted seeks approval in the "treatment of patients with metastatic carcinoma of the ovary who are refractory to both paclitaxel- and platinum-based chemotherapy regimen (b) (4) [redacted]".

Two studies were conducted by the sponsor in order to characterize the pharmacokinetics of Doxil. One of the studies was a Phase II clinical trial (study 30-22) conducted in the targeted population for the purpose of characterizing the pharmacokinetics of Doxil in ovarian cancer patients. The second study submitted is a population pharmacokinetic analysis study involving pharmacokinetic data from 120 patients (81 males, 39 females) from 10 different clinical trials. A second clinical trial was submitted by the sponsor in breast cancer patients (30-17); however no pharmacokinetic data results were submitted. The sponsor stated that the pharmacokinetic results of the study (30-17) were pooled with the data utilized in the population analysis. The Phase II trial in the ovarian population (study 30-22) was part of the 10 trials utilized for the population pharmacokinetic analysis. Plasma samples were analyzed using a validated HPLC method with fluorescence detection that did not distinguish liposome-encapsulated doxorubicin from nonliposomal doxorubicin. The same assay was used to characterize Doxil and doxorubicinol in the original NDA for the AIDS-related Kaposi's sarcoma indication; however the same assay methodology was only able to partially validate the determination of doxorubicinol in human plasma samples in this supplement.

Assay Methodology [redacted] (b) (4), **appendix F, Vol. 4)** The assay method used for NDA 50718 (AIDS-related Kaposi's sarcoma) is the same as the method employed for the new pharmacokinetic studies submitted and the population pharmacokinetic analysis in this submission. The linear range of the assay for doxorubicin and doxorubicinol was established between 0.005 to 1.00 μg/mL, with a lower limit of quantitation (LLOQ) of 0.01μg/mL. The developed assay does not distinguish liposome-encapsulated doxorubicin from nonliposomal doxorubicin. Daunarubicin was used as the internal standard at a constant concentration of 0.630 μg/mL in all samples. Please refer to **Appendix B** for additional information.

Reviewer's comment:
The same assay was employed for the submitted studies to Doxil's new indication; however the assay method was only able to partially validate the determination of doxorubicinol in human plasma samples. Please address the disparity observed in validating the determination of doxorubicinol between the original NDA and sNDA submissions even though the same assay was used.

Population Pharmacokinetic Study
The input data file necessary to run the population pharmacokinetic analysis used by the sponsor and the one submitted to the Agency to use for our analysis and verification are different. Study number/tumor type were not provided in the data input file. As a result, the Agency can not verify even the most basic of all the models submitted (i.e., the pharmacokinetic model) due to our results being significantly different from the sponsor's. Additional details are provided below with additional comments on the quality of the data that was submitted.

1. *Model H isolated study numbers 2,3, and 4 and compared them to the remaining studies with a considerably better fit observed per drop in objective function of over 500 points. The effect of gender on volume of distribution (V_D) was also instrumental in the observed improvement of data fit.*
   - *We need the data input file with the study site/tumor type as a covariate studied.*
   - *The files submitted do not reflect bilirubin being investigated as a possible covariate, why?*
   - *Why was study 30-22 not compared to the Pop PK analysis to investigate whether the PK of Doxil behaves the same or differently across cancer populations?*
2. *The sponsor can not detect doxorubicinol in this submission utilizing the same assay employed in the original NDA with Doxil doses ranging from 50 to 60 mg/m^2, yet the KS package insert describes doxorubicinol being detected at Doxil doses of 10 to 20 mg/m^2? Please clarify.*
3. *Error in the data input file: Patient* [redacted] (b) (6) *had a line listing for MDV of 1 instead of 0. That correction has been made.*

The sponsor describes table 3 of their summary as a list of the parameter estimates from various structural models fitted to the data. Model A is a 1-compartment open model, model B is a 2-compartment open model and model C is a 2-compartment open model with non-linear elimination. Based on improvements in the objective function of the model and improvements on median absolute normalized prediction error (MDAPE) and median normalized prediction error

(MDPE) estimates, the 2-compartment non-linear model was chosen as the best model (model C).

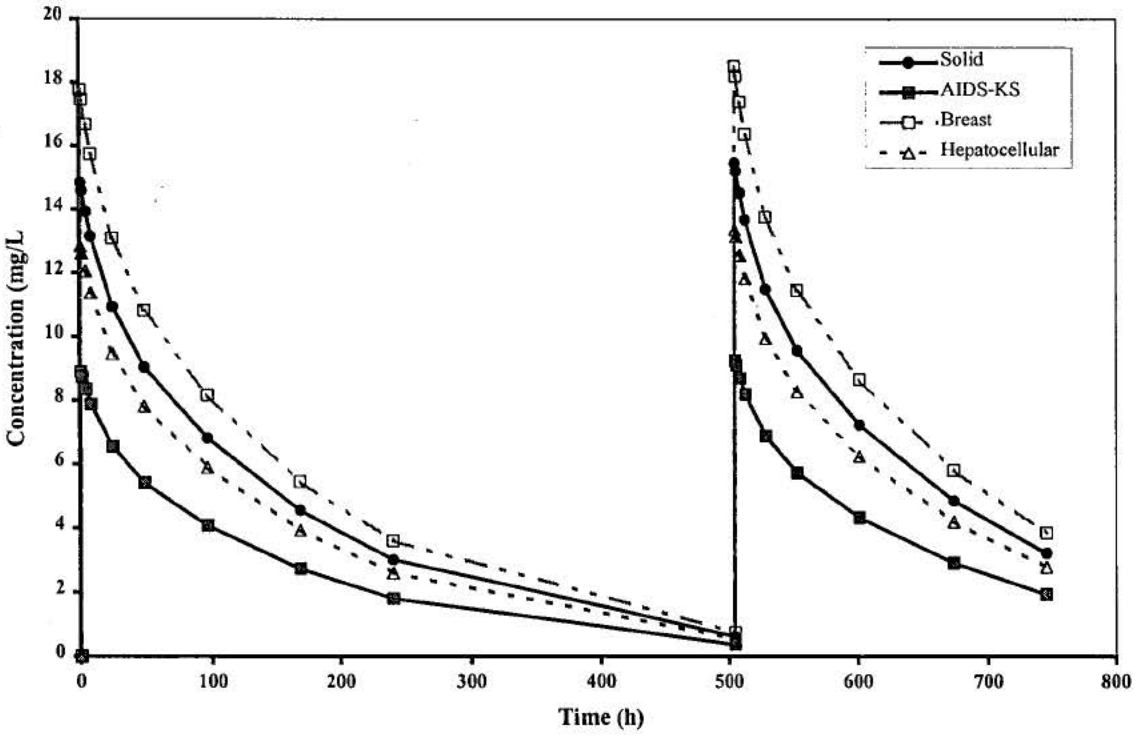
Models A to C were not submitted for review to allow the reviewer an opportunity to assess the process utilized to obtain the conclusions described.

The sponsor describes differences observed in the pharmacokinetic parameters of the AID-KS patients (study 30-14) and argues that this could be partially due to the fact that the plasma samples from these patients were analyzed in a different laboratory to the rest of the patients.

Another possibility is that this population typically is under multiple drug therapy with medications that have a high potential for drug-drug interactions. Investigating through population analysis the possibility of drug interactions being a worthy covariate in this study site should be considered.

The sponsor states that the approximate 2-fold difference seen in Figure 6b below of their summary of simulated concentrations due to tumor type effect in the two extreme cases will probably not result in any serious toxicity that would require changes in dosing schemes.

Figure 6b. Simulation of Concentration-time Curve for Tumor Type Effect



1. *The simulations seem to have been carried out to two cycles, not sufficiently far out enough to assess any long term effects due to tumor types.*

2. *Simulation data will have to be submitted in order for the Agency to assess the appropriateness of the simulations, verification of the simulations, and their applicability in this setting.*

NOTE: *Simulation demonstrating lack of drug accumulation with repeated drug administration seems to have a trend toward drug accumulation however so slight. Unable to assess at this time due to incorrect input file submission for the Population pharmacokinetics.*

Pharmacokinetic Study in the targeted population (US 30-22)
Overall Study Design and Plan

This was a Phase II, noncomparative, multicenter study to determine the safety, pharmacokinetics, and response to Doxil in patients with recurrent or persistent epithelial ovarian carcinoma who had received initial treatment with both platinum-based and paclitaxel-based treatment regimens. Patients were started at 50 mg/m^2 Doxil every 3 weeks. The dose of 50 mg/m^2 was selected on the basis of the results of a Phase I MTD study in solid tumors. Pharmacokinetic data were to be collected at specified intervals during the first two treatment cycles.

- Study Objectives

This study was designed to evaluate:
1. the pharmacokinetics of Doxil in patients with epithelial ovarian cancer, and
2. the response to Doxil in patients with epithelial ovarian cancer who have failed treatment with both platinum-based and paclitaxel-based regimens.

The investigators made one routine modification to the protocol instructions for the administration of the first dose, the initial rate of infusion was reduced to 1 mg/min, and then increased after the first 30 minutes if this was uneventful, to complete the infusion over 1 hour. Premedication was left to the choice of the investigators, but they used 100 mg IV of hydrocortisone, 25 mg of diphenhydramine, and 300 mg of cimetidine routinely to avoid the occasional acute infusion reaction.

- Concomitant Medications

Local or systemic cytotoxic chemotherapy for ovarian carcinoma other than Doxil was not allowed while patients were enrolled in study. Premedication was at the discretion of the investigator. Colony stimulating factors (e.g., G-CSF) were not to be used before the first treatment dose or until after the administration of the second dose of Doxil. Subsequent use of colony stimulating factors or erythropoietin was permitted. Patients were not allowed to undergo radiotherapy of any lesion, including those which were nonevaluable or unmeasurable, while enrolled in this study. If symptoms of palmar-plantar erythrodysesthesia (PPE) occurred, oral pyridoxine (vitamin B-6, 50 mg TID) was recommended

for at least 1 week. Patients were not to receive any other investigational drugs while enrolled in the study.

- On-Study Evaluations

Blood samples (8 mL minimum volume) were obtained from patients for drug concentration measurement immediately prior to the infusion and at the following times: end of infusion, 30 minutes, 3 hours, 5 hours, 28 hours, 96 hours (day 4), 384 hours (day 16), and 504 hours (day 21, prior to next infusion). The drug concentration measurements were carried out for the first 2 cycles of treatment; additional measurements beyond the first 2 cycles were at the discretion of the investigator and the sponsor. If ascities or a pleural effusion was present, a blood sample (minimum volume 5 mL) was obtained from the patient 1 hour post infusion unless medically contraindicated.

A more appropriate sampling approach to mirror the drug's elimination around Doxil's half-life (about 70 hours according to the population PK analysis) may have provided more useful information that could be readily applied to drug therapy.

- Drug Concentration Measurements

Blood samples were collected in EDTA-containing tubes and immediately centrifuged to separate the plasma which was frozen for subsequent HPLC analysis for total doxorubicin and its primary metabolite, doxorubicinol. Results were analyzed for determination of pharmacokinetic parameters using pharmacokinetic modeling techniques.

- Pharmacokinetic Analysis

Blood samples for drug concentration measurements were taken from 11 patients, during the first two cycles or in selected subsequent cycles. These results were analyzed for determination of pharmacokinetic parameters in conjunction with patient results from other studies of Doxil using population modeling techniques. Total doxorubicin was measured in plasma by an analytical method used previously in the original NDA for the determination of doxorubicin and doxorubicinol in human plasma . Further details on the assay used are located in the "Assay Methodology" section of this review.

- Pharmacokinetics

For the studied dose, 50 mg/m^2, the pharmacokinetics of Doxil were best described by an open, two compartment structural model, with linear distribution between the central and peripheral compartments and a nonlinear elimination from the central compartment. These findings are different from the earlier pharmacokinetic results of Study 30-14 (a randomized, cross-over pharmacokinetic and tumor localization study of DOXIL in 43 patients with AIDS-related Kaposi's sarcoma; Doxil was dosed at 10 mg/m^2 and 20 mg/m^2 for 2 cycles with a 3-week interval between cycles). Since only doses of 10 and 20 mg/m^2 were evaluated, Study 30-14 did not reveal the nonlinearity of Doxil pharmacokinetics. However, in Study 30-22 with a dose of 50 mg/m^2 , the disappearance rate of total doxorubicin from the plasma decreased. The other pharmacokinetic parameter values from this recent analysis (e.g., volume of distribution, distributional

clearance) were unchanged from the earlier results of Study 30-14. The pharmacokinetic results are provided in the table A below.

Table A: Pharmacokinetic Parameter Estimates

Statistic n = 9	Vss (L/m 2)	CLi (L/h/m 2)	Km (mg/L)	AUC (mg/L • h)
Mean	2.98	0.0745	2.84	3574
CV%	16.2	47.3	68.1	47.0
Median	3.12	0.0725	2.13	3531
Minimum	2.20	0.0269	1.67	957
Maximum	3.58	0.148	7.89	6741

Vss – volume of distribution at steady-state, CLi – intrinsic clearance, Km – Michaelis Menton Constant.

In patients with ovarian cancer, Doxil displays nonlinear pharmacokinetics, and does not accumulate with dosing frequencies of ≥ 3 weeks. For additional study details, please refer to **Appendix C**.

Reviewer's comments:

1. *A table comparing the pharmacokinetic differences between study 30-22 and previous study 30-14 was not provided.*

2. *Verification of the pharmacokinetic profile of Doxil in this study (the targeted population) by the Agency was not possible at this time due to the submission of the wrong input file in the population pharmacokinetics study by the sponsor.*

3. *A comparison of the pharmacokinetic parameters of Doxil in the targeted population from study 30-22 are provided below. The pharmacokinetic parameters listed below in Table 1 are different from the pharmacokinetic parameters listed in the summary above in table A. It is unclear which data set is being reflected in the results above. However, the sponsor is claiming that the population pharmacokinetic parameters obtained from the analysis are the same as the population pharmacokinetic parameters from study 30-22. Please clarify.*

Table 1 **Summary Pharmacokinetic Estimates for Female Patients from Study 30-22**

Statistic n = 11	Cmax (mg/L)	Vss (L/m^2)	CLi ($L/h/m^2$)	Km (mg/L)
Mean	32.9	2.19	0.0112	12.3
CV%	18.7	14.4	37.9	31.9
Median	34.7	2.18	0.0272	11.7
Minimum	18.6	1.46	0.0131	6.58
Maximum	41.1	2.66	0.0494	19.1

Cmax – maximum plasma concentration; Vss – volume of distribution at steady-state;

CLi – intrinsic clearance; Km – Michaelis-Menton Constant.

4. *In the PK summary table entitled "PK Summary Stats 40, 45, 50" from the submitted 3.5 disk, the sponsor's PK parameters listed and the parameters for the Pop PK summary are different. Please clarify which data set the PK summary stats 40, 45, 50 corresponds to (located in the floppy disc originally submitted).*

5. *The new population pharmacokinetic parameters from the new population pharmacokinetic summary in volume 14 (Table 7, page 27) does not match the two sets of pharmacokinetic parameters previously discussed (PK Summary Stats 40, 45, 50 and the table A above). Please clarify. Table 7 from volume 14 is depicted below.*

Table 7.

Statistics of Bayesian Pharmacokinetic Parameter Estimates (Model H; FOCE method)

n=120	Primary parameters					Derived parameters				
	Vmax ($mg/h/m^2$)	K (mg/m^2)	K_{12} (/h)	K_{21} (/h)	V_1 (L/m^2)	Km[a] (mg/L)	Cli[b] ($L/h/m^2$)	CL_2[c] ($L/h/m^2$)	Vss[d] (L/m^2)	Half life[e] (h)
Minimum	0.325	12.12	0.006	0.042	0.96	4.59	0.008	0.003	1.10	23.53
Maximum	0.773	90.26	0.017	0.042	3.85	65.81	0.152	0.011	3.91	230.77
Median	0.540	40.77	0.011	0.042	1.86	22.39	0.024	0.006	2.00	70.20
Mean	0.547	41.93	0.011	0.042	1.93	24.08	0.030	0.006	2.07	73.86
CV%	15	31	14	---	31	45	72	31	27	37

[a] $Km = K / V_1$
[b] $CLi = Vmax / Km$
[c] $CL_2 = K_{12} / V_1$
[d] $Vss = V_1 + V_2$
[e] Half life is the apparent half life at concentrations of doxorubicin far below Km concentration.

Case Study: Doxil PK in a patient with High bilirubin levels (Appendix D, Vol. 4 what type of cancer did this patient have?)

The effect of liver impairment on the pharmacokinetics of doxorubicin following Doxil was studied in a patient with cutaneous Kaposi's Sarcoma and a BSA = 2.0 m^2. The predose and average (over a 3 week cycle) total bilirubin value was 21.7 and 11.4 mg/dL, respectively. The recommended dose for this treatment is 20 mg/m^2, however, using the Adriamycin guidelines for dose adjustments the dose was reduced by 75% to 5 mg/m^2. Three weeks later the patient's total bilirubin decreased to a predose and average (over a 3-week cycle) value of 16.6 and 7.29 mg/dL, respectively. The full recommended dose of 20 mg/m^2 was administered at this cycle. Serial plasma samples were obtained after each dose and analyzed for total plasma doxorubicin. The pharmacokinetics after each Doxil cycle were generated using compartmental analysis via the ADAPT II, Release 4.0 Pharmacokinetic/Pharmacodynamic Systems Analysis Software. Descriptive pharmacokinetic parameter estimates are reported and compared between cycles and literature values in a similar patient population.

Results

The plasma concentration versus time data was best modeled using a one-compartment model with first order (linear) elimination; the fitted pharmacokinetics parameters were the volume of distribution at steady-state (Vss) and the total plasma clearance (CLt). However, the model was not verifiable because the sponsor did not submit the data. The maximum concentration was obtained by direct observation of the data, and the half-life and area-under the curve (AUCss) were both calculated using the appropriate equations. Figure 1, depicts the fit of the pharmacokinetic model to the observed data. Figure 2 depicts the dose-normalized concentrations for each dose level. The 20 mg/m^2 dose provided a larger AUCss. This difference could be attributed to the inter-occasion variability in the pharmacokinetics within this patient, i.e., one cannot assume that the clinical status of the patient remains unchanged. Also, it is known that Doxil displays nonlinear pharmacokinetics at doses approaching 40 mg/m 2, that is, a doubling in dose will give rise to a dis-proportionate increase in both concentrations and AUC. Consequently, as the dose is increased from 5 to 20 mg/m^2 one would expect a slightly larger AUCss as observed in this patient. The dose-normalized AUCss following the 5 mg/m^2 dose, (total bilirubin = 11.4 mg/dL) did not exceed the AUCss at the 20 mg/m 2 dose (total bilirubin was 7.29 mg/dL), as one would expect if liver impairment had an effect on elimination of doxorubicin. No doxorubicinol was detected at any time point at either dose level. Table 1 displays the pharmacokinetic values at both dose levels in this patient and literature values in patients with Kaposi's Sarcoma and normal total bilirubin values.

Table 1

	Dose Administered	Dose Administered	Literature 1 : Median (Range)
Parameter	5 mg/m 2	20 mg/m 2	20 mg/m 2
Vss (L/m 2)	2.01	1.49	2.75 (1.39–8.79)
CLt (L/h/m 2)	0.0482	0.0289	0.0351 (0.0143–0.576)
Half-life (h)	28.9	35.8	54.5 (10.6–108)
Cmax (mg/L)	2.45	13.1	8.47 (2.50–16.5)
AUCss (mg/L•h)2	20.6	34.6	28.5 (1.74–69.8)

1 Published Values – Clinical Pharmacology and Therapeutics 1997;61:301–11, 2 AUCss is normalized to a 1 mg/m 2 dose

Extrapolation to a dose of 50 mg/m^2 is not possible because nonlinearity takes place somewhere between the 20 and 50 mg/ m^2 dose. Dose adjustment did take place in the patient receiving the 5 mg/m^2 dose however. It is unclear why the sponsor believes that no dosage adjustment would be necessary for the 50 mg/ m^2 dose (2.5 times the 20 mg/m^2).

The assumption that the information provided from this case report can be extrapolated to a dose 1.5 to 2.5 times what was actually administered is scientifically unsound. The sponsor has stated that the pharmacokinetics of Doxil at higher doses than the KS indication have demonstrated nonlineriarity. Predicting pharmacokinetics with 1.5 to 2.5 times the dose administered in a possibly compromised liver as demonstrated by elevated bilirubin levels should not be done. (b) (4)

As mentioned earlier in the review of Study 30-22 when comparing the results to study 30-14 in AIDS KS patients: since only doses of 10 and 20 mg/m^2 were evaluated, Study 30-14 did not reveal the nonlinearity of Doxil pharmacokinetics. However, in Study 30-22 with a dose of 50 mg/m^2, the disappearance rate of total doxorubicin from the plasma decreased.

Please refer to the appendix for further information on the submitted case report.

Figure 1

Total Doxorubicin Plasma Concentrations Following Administration of DOXIL 5 mg/m^2 and 20 mg/m^2 in One Patient on Separate Occasions

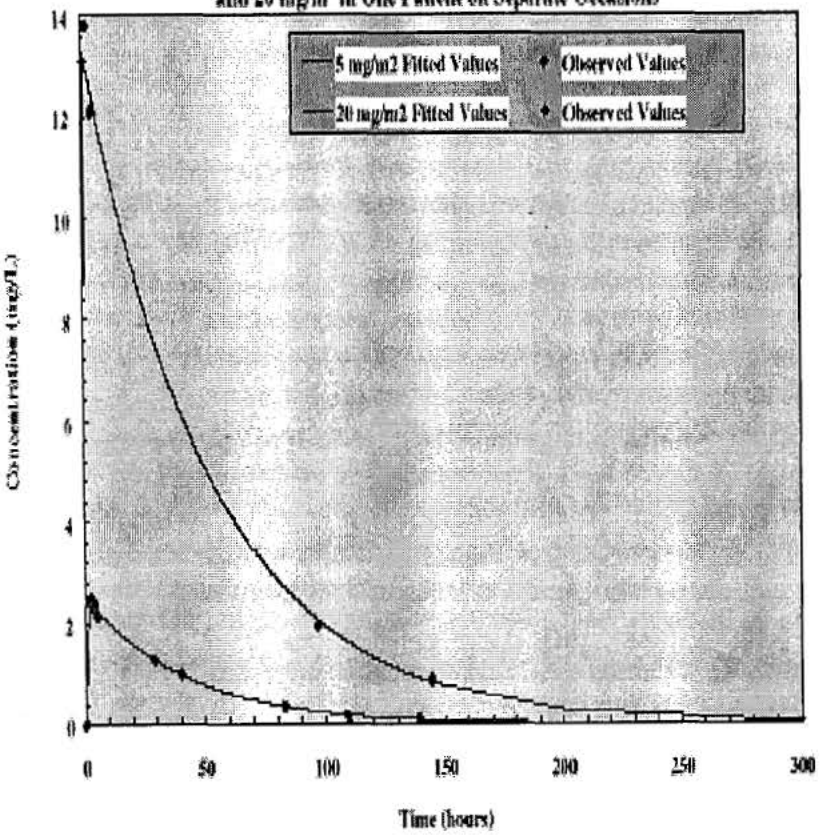
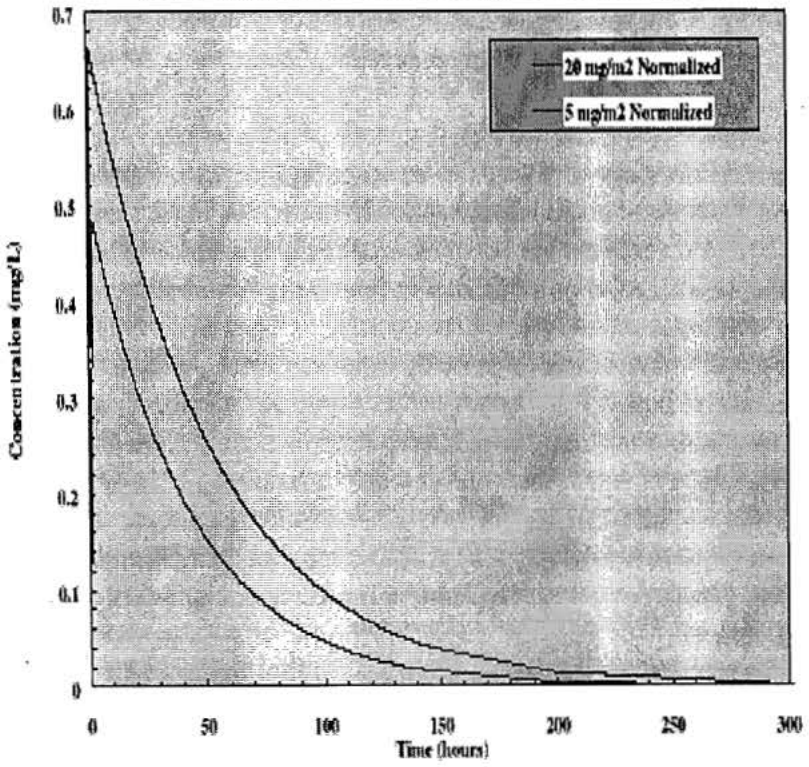


Figure 2

Normalized Total Doxorubicin Plasma Concentrations Following Administration of DOXIL 5 mg/m2 and 20 mg/m2 in One Patient on Separate Occasions



PK study (30-17) in breast cancer patients (Make sure it wasn't used for the Package insert)

This study (in breast cancer patients) was not reviewed because specific pharmacokinetic results were not submitted. The pharmacokinetic information obtained from this study was pooled with the data utilized for the population pharmacokinetic analysis conducted in this application with no means of identifying this data set.

Comments to the sponsor

1. Assay Methodology: The assay used for the original NDA was employed for the supplemental NDA for Doxil's new indication; however the assay method was only able to partially validate the determination of doxorubicinol in human plasma samples. Please address the disparity observed between the NDA and sNDA submissions even though the same assay was used.
   - The sponsor can not detect doxorubicinol in this submission utilizing the same assay employed in the original NDA with Doxil doses ranging from 50 to 60 mg/m^2, yet the KS package insert describes doxorubicinol being detected at Doxil doses of 10 to 20 mg/m^2. Please clarify.

2. Population Pharmacokinetic Study:
   - The data input file with the study site/tumor type as a covariate studied needs to be submitted.
   - The files submitted do not reflect bilirubin being investigated as a possible covariate, why?
   - Study 30-22 should be compared to the Population pharmacokinetic analysis study performed to investigate whether the pharmacokinetics of Doxil behaves the same or differently across cancer populations. The final model should be appropriately presented with supportive raw data and input files. The data from study 30-22 should be submitted to the Agency in a way that will allow for verification of the raw data.
   - The sponsor states that the approximate 2-fold difference observed in Figure 6b of their summary of simulated concentrations due to tumor type effect in the two extreme cases will probably not result in any serious toxicity that would require changes in dosing schemes. The simulations seem to have been carried out to 1.5 cycles, not sufficiently far out enough to assess any long term effects due to tumor types. Simulation data will have to be submitted in order for the Agency to assess the appropriateness of the simulations, verification of the simulations, and their applicability in this setting

3. Pharmacokinetic Study in the targeted population: A comparison of the pharmacokinetic parameters of Doxil in the targeted population from study 30-22 were provided. The pharmacokinetic parameters listed in Table 1 above are different from the pharmacokinetic parameters listed in the summary above in table A. It is unclear which data set is being reflected in the results. However, the sponsor is claiming that the population pharmacokinetic parameters obtained from the analysis are the same as the population pharmacokinetic parameters from study 30-22. Please clarify.

- The protocol states that patients with ascites or a pleural effusions would undergo an additional blood sample collection (minimum volume 5 mL) 1 hour post infusion. At the advisory committee meeting on June 8th, 1999, the sponsor stated that 5 patients had ascites during the clinical trials. Please provide the pharmacokinetic data for those 5 patients and/or a means of identifying those patients in the electronic data sets for analysis purposes if available.

- During the advisory committee meeting, much deliberation took place regarding the appropriate phase 3 trial to be conducted for the full approval of Doxil in the targeted population. Characterizing the pharmacokinetics in the targeted population with the correct dose and regimen should be part of the objectives of the trial. As mentioned at the advisory committee meeting, patients with ascites and malignant pleural effusions may be encountered in the community at a greater frequency than was observed during the clinical trials. As a result, the pharmacokinetics in this subpopulation should be investigated due to the safety concerns expressed at the advisory committee meeting. It may very well be that the pharmacokinetics of Doxil are quite different in patients with ascites or malignant pleural effusions. Since the previous indication's pharmacokinetics was conducted in a predominantly male population, a pharmacokinetic analysis will also resolve any gender related issues associated with Doxil.

4. Electronic data submitted: In the pharmacokinetic summary table entitled "PK Summary Stats 40, 45, 50" from the submitted 3.5 disk, the sponsor's pharmacokinetic parameters listed and the parameters for the population pharmacokinetic summary are different. Please clarify which data set the "PK summary stats 40, 45, 50" corresponds to (located in the floppy disc originally submitted).

5. New Population Pharmacokinetic analysis submitted data (Vol. 14): The new population pharmacokinetic parameters from the new population pharmacokinetic summary in volume 14 (Table 7, page 27) does not match the two sets of pharmacokinetic parameters previously discussed (PK Summary Stats 40, 45, 50 and table A above). Please clarify. Table 7 from volume 14 is depicted above.

6. Case Study: Doxil pharmacokinetics in a patient with high bilirubin levels (Appendix D, Vol. 4): The assumption that the information provided from this case report can be extrapolated to a dose 2 to 2.5 times is scientifically unsound. The sponsor has stated that the pharmacokinetics of Doxil at higher doses than the KS indication have demonstrated nonlinearity. Predicting pharmacokinetics of 1.5 to 2.5 the dose administered in a possibly compromised liver as demonstrated by elevated bilirubin levels should not be done. (b) (4)

Sponsor's Proposed Labeling:

(b) (4)

[redacted] (b) (4) the following statement should be included in the package insert.

In the Box Warning include-

Due to nonlinear pharmacokinetics of Doxil at 50 mg/m2 dose, a small change in dose may result in a non proportional larger change in the elimination half-life and exposure (AUC) to the drug.

In the Pharmacokinetic sub-section include-

The pharmacokinetics of Doxil at 50 mg/m2 dose is reported to be nonlinear. At this dose, the elimination half-life of Doxil is expected to be longer and the clearance is expected to be lower compared to 20 mg/m2 dose. The exposure (Area under the curve) is expected to be more than proportional at 50 mg /m2 dose when compared with the lower doses.

The proposed labeling is located in **Appendix A**.

Recommendation to the Clinical Division: The supplemental application is deficient from the Clinical Pharmacology and Biopharmaceutics perspective. The sponsor should submit the clinical pharmacokinetic data as a Phase IV commitment for Agency review and for incorporation of adequate Clinical Pharmacology information in the package insert.

Recommendation to the sponsor: Please forward the above comments and our recommendation to the clinical division and to the sponsor.

Lydia Velazquez Kieffer, Pharm.D.
Reviewer 6-9-99
Division of Pharmaceutical Evaluation I

Atiqur Rahman, Ph.D. 6/18/99
Team Leader
Division of Pharmaceutical Evaluation I

cc: IND 36,778
NDA 50,718
HFD-150/ Division File
HFD-150/ ADunson, GWilliams, GFrykman
HFD-150/DYLeeHam, PAndrews
HFD-850/ LLesko
HFD-860/ MMehta, ARahman, LVelazquezKieffer
CDR BMurphy

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 50-718/S-006

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEETING MINUTES

Catterson

MEETING DATE: August 20, 1998 **TIME:** 12:00pm **LOCATION:** Conf. Room I

IND#: 36,778; NDA 50-718

Meeting Request Submission Date: June 22, 1998
Briefing Document Submission Date: July 13, 1998
Additional Submission Date: August 6, 1998

DRUG: DOXIL® (doxorubicin HCl liposome injection)

SPONSOR/APPLICANT: SEQUUS Pharmaceuticals, Inc.

TYPE OF MEETING:

1. Pre-NDA for sNDA

2. **Proposed Indication:** (b) (4) (b) (4)

FDA PARTICIPANTS:

Robert Temple, M.D.	----	Director, Office of Drug Evaluation I
Robert Justice, M.D.	----	Acting Director, Division of Oncology Drug Products
Julie Beitz, M.D.	----	Acting Deputy Director
Grant Williams, M.D.	----	Medical Team Leader
Isagani Chico, M.D.	----	Medical Reviewer
Gang Chen, Ph.D.	----	Biometrics Team Leader
Chengyi Liang, Ph.D.	----	Chemistry Reviewer
Alvis Dunson	----	Project Manager
Patrick Guinn	----	Project Manager

FDA PARTICIPANTS (Pre-Meeting Only):

James Krook, M.D.	----	Member, Oncol. Drugs Advis. Com. (via teleconference)
Leslie Vaccari	----	Special Assistant to the Division Director

INDUSTRY PARTICIPANTS:

Ken Cunningham, M.D.	----	Vice President & Medical Director
Michele Jumper, Ph.D.	----	Manager, Regulatory Affairs
Timothy Mulligan, M.D.	----	Director, Clinical Research
Aron Stein, Ph.D.	----	Vice President, Regulatory Affairs
Barbara Gunthe	----	Regulatory Manager

MEETING OBJECTIVE:

Sequus Pharmaceuticals, Inc. has requested this second Pre-NDA meeting to discuss their proposed Supplemental NDA for the use of DOXIL for the [redacted] (b) (4) [redacted] The sponsor would like to further discuss issues raised at their Pre-NDA meeting held on June 19, 1998, and their plans to terminate their European second-line ovarian trial, Study 30-57.

SPONSOR'S QUESTION #1:

When defining available therapy for a patient population for accelerated approval, should the regulations and guidelines be interpreted as referring only to those drugs which are indicated for the specific disease and patient population?

FDA ANSWER:

- Our policy is under development. Available therapy generally refers to the labeled indications. If there were a substantial body of literature suggesting effective unlabeled therapy, it may be used to identify "available therapy" even if it is not yet labeled for the specific indication.

- If there is available therapy for an indication, then your drug must have a clearly higher objective response rate or alternatively, your drug could demonstrate a similar response rate with some toxicity advantage than the available therapy in the proposed population.

- In the case of etoposide, we do not feel there is a substantial body of literature suggesting benefit in the setting of 'ovarian cancer refractory to a taxane and a platinum compound'. Therefore, we do not consider etoposide as "available therapy" for this indication and your phase II data are sufficient for filing an NDA for this indication. However, the question of whether the data are reasonably likely to predict clinical benefit would be decided after full review and advice from the Oncology Drugs Advisory Committee.

- Your application would be strengthened if data from the interim analysis of response rates of Study 30-49 were submitted with the NDA (targeted for November 1998).

SPONSOR'S QUESTION #2:

Does the FDA agree that [redacted] (b) (4) patients have an unmet medical need?

FDA ANSWER:

- Yes.

SPONSOR'S QUESTION #3:

Is it acceptable to terminate Study 30-57 at the first interim analysis of 100 evaluable patients?

FDA ANSWER:

- It is acceptable to terminate Study 30-57, however, you are still required to submit study reports.

SPONSOR'S QUESTION #4:

Assuming DOXIL demonstrates equivalent efficacy and a safety advantage in Study 30-49, does the Division agree that completion of Study 30-57 is not critical to registration in the United States?

FDA ANSWER:

- Please refer to the Meeting Minutes dated 7/12/98. The Agency minutes state that:

  "Hycamtin should be included as a comparative drug and time-to-progression should be the primary endpoint. If this trial demonstrates superiority, the one phase III trial accompanied by data from phase II studies in patients with refractory advanced ovarian cancer will be adequate for submission and may qualify for a regular approval..."

  "If this trial fails to show superiority but demonstrates a similar response rate with some toxicity advantage, then accelerated approval could be considered based on one completed Phase 3 trial and a Phase 4 commitment to conduct a confirmatory trial post approval..."

- Recently Taxol was approved in combination with cisplatin as first-line therapy of ovarian cancer on the basis of a survival advantage over cyclophosphamide and cisplatin. The potential implications of this change in the definition of standard first-line therapy should be considered. Your study enters patients who have received first-line platinum based chemotherapy. The protocol should be amended to require patients to have received a platinum compound and Taxol. If a substantial proportion of the patients in study 30-49 have received Taxol and a platinum compound, then the minutes quoted above are still operative, and demonstration that Doxil is equivalent in efficacy to topotecan with a safety advantage could support accelerated approval.

- If Doxil receives accelerated approval on the basis of data from single-arm trials for platinum-refractory, taxane-refractory ovarian cancer, then Study 30-49 could serve as the phase IV study if it demonstrates that Doxil produces a significantly longer time-to-progression than topotecan. If, after review, the data from single-arm studies does not produce sufficient

evidence for accelerated approval, then Study 30-49 may support accelerated approval as outlined in the minutes above. In this case, unless Doxil demonstrated superiority to topotecan in time-to-progression or survival, a Phase 4 commitment to conduct a confirmatory trial post-approval would be needed.

The meeting was concluded at 1:30pm. There were no unresolved issues or discussion points.

Debra M. Catterson 8/24/98
Debra Catterson, R.Ph.
Minutes Preparer

Concurrence Chair: Isagani Maria Chico 8/25/98
Isagani Chico, M.D.
Medical Reviewer

cc: Original IND 36,778/NDA 50-718
HFD-150/Div Files
HFD-150/DPease
HFD-150/LVaccari
HFD-150/DCatterson/8.24.98

MEETING MINUTES

Catterson

MEETING MINUTES

MEETING DATE: June 19, 1998 **TIME:** 1:00pm **LOCATION:** Conf. Room I

IND#: 36,778; NDA 50-718

Meeting Request Submission Date: Feb. 27, 1998
Briefing Document Submission Date: May 22, 1998

DRUG: DOXIL® (doxorubicin HCl liposome injection)

SPONSOR/APPLICANT: SEQUUS Pharmaceuticals, Inc.

TYPE OF MEETING:

1. Pre-NDA for sNDA

2. **Proposed Indication:** Treatment of patients with metastatic carcinoma of the ovary who are refractory to (b) (4)

FDA PARTICIPANTS:

Robert Temple, M.D.	----	Director, Office of Drug Evaluation I
Robert Justice, M.D.	----	Acting Director, Division of Oncology Drug Products (DODP)
Grant Williams, M.D.	----	Medical Team Leader
Isagani Chico, M.D.	----	Medical Reviewer
Gang Chen, Ph.D.	----	Biometrics Team Leader
Masahiro Takeuchi, Ph.D.	----	Biometrics Reviewer
Liang Zhou, Ph.D.	----	Chemistry Team Leader
Lydia Kieffer, Pharm.D.	----	Biopharmaceutics Reviewer
Patricia Delaney	----	Public Health Specialist, Office of Special Health Issues
Patrick Guinn	----	Project Manager

FDA PARTICIPANTS (Pre-Meeting Only):

Rachel Behrman, M.D.	----	Deputy Director, Office of Drug Evaluation I
Robert Ozols, M.D., Ph.D.	----	Member, Oncol. Drugs Advis. Com. (via teleconference)
Atik Rahman, Ph.D.	----	Biopharmaceutics Team Leader

INDUSTRY PARTICIPANTS:

Randy Allred, Dr.P.H.	----	Sr. Director, Biostatistics, Stat. Programming, and Data Mgt.
Ken Cunningham, M.D.	----	Vice President & Medical Director
Craig Henderson, M.D.	----	Chief Executive Officer
Michele Jumper, Ph.D.	----	Manager, Regulatory Affairs
Aron Stein, Ph.D.	----	Vice President, Regulatory Affairs
Craig Tendler, M.D.	----	Director, Oncol. Research, Schering-Plough Research Institute
William P. McGuire, M.D.	----	Clin. Prof. of Medicine, Univ. of Miss. School of Medicine

MEETING OBJECTIVE:

Sequus Pharmaceuticals, Inc. has requested this Pre-NDA meeting to discuss their proposed Supplemental NDA for the use of DOXIL for the treatment of patients with metastatic carcinoma of the ovary who are refractory to (b) (4) The sponsor plans to present data from one primary and three supportive efficacy studies and believes that the data are sufficient to support accelerated approval.

SPONSOR'S QUESTION #1:

(b) (4) refractory ovarian patients have an unmet medical need. Does the Agency concur?

FDA ANSWER:

- **Yes, safe and effective drugs are needed for patients with (b) (4) refractory ovarian cancer (patients who progressed while receiving treatment or recurred within six months of platinum compound, taxol, (b) (4)**

SPONSOR'S QUESTION #2:

DOXIL meets the unmet medical need as:

1. Recurrent ovarian cancer patients who have failed existing therapies have few or no treatment options.

2. The response rates to DOXIL in triple-refractory ovarian cancer patients (Study 30-47) appear to be comparable to those seen with approved agents in patient populations that have failed single and double therapies.

3. DOXIL has a well-defined safety profile in over 700 solid tumor patients and over 2000 AIDS-KS patients. The risk of life-threatening adverse events is minimal.

4. Comparative data from an interim safety analysis from Study 30-49 will support DOXIL safety.

Does the Agency concur?

FDA ANSWER:

- **There is an unmet need to show significant activity in (b) (4) refractory patients. Showing tumor response in a significant number of (b) (4) refractory patients who have few or no options could be adequate for approval under the accelerated approval mechanism. However, 5 responses in 38 patients (13%) is probably not adequate evidence of benefit. A database approximately 2 times this size would be needed and a higher response rate would be desirable.**

- **If Sequus establishes that secondary refractory patients have an unmet need*, then the described database may be adequate for filing for accelerated approval.**

*** Definition of unmet need**

- Available meaning only available therapy?

- Comparability of etoposide database or other databases

SPONSOR'S QUESTION #3:

The efficacy data including the following:

1. Anticipated response rates of 10%-20% in approximately 35 evaluable (b) (4) refractory patients
2. Supportive efficacy data from other ovarian patient populations
3. Analysis of clinical benefit of response

are sufficient to support accelerated approval for the following indication: "Treatment of patients with metastatic carcinoma of the ovary who are refractory to (b) (4)."

Does the Agency concur?

FDA ANSWER:

- **No. The proposed indication should be for patients with ovarian cancer refractory to platinum, taxol (b) (4).**
- **See answer to question #2.**

SPONSOR'S QUESTION #4:

The content and structure of the safety database will support the proposed dosing regimen. Does the Agency concur?

FDA ANSWER:

- **Yes.**

SPONSOR'S QUESTION #5:

Sufficient pharmacokinetic data will be provided to support the proposed dosing regimen. Does the Agency concur?

FDA ANSWER:

- **Yes. All the listed Pharmacokinetic studies in Table 9 of Topic 4 will provide sufficient pharmacokinetic data to support the proposed dosing regimen.**
- **The studies should be well conducted and documented to support the claim.**

Additional PK Comments:

1. **It appears that study 30-22 is a pharmacokinetic study in the targeted population according to Table 9 of Topic 4 of the submitted package. However, appendix D has a publication of study 30-22 that contains no pharmacokinetic information. Will the data be submitted at a later date?**

   Yes.

2. **The sponsor** [redacted] (b) (4)

3. **Does the sponsor have any pharmacokinetic cardiotoxicity data?**

   No.

4. **A copy of section 8.3 (Clinical Pharmacology) should be included in section 6.**

5. **A dose proportionality summary from all the studies in Table 9 (from 20 to 60 mg/m^2) should be submitted.**

6. **Electronic data transmission information format will be forwarded to the sponsor.**

SPONSOR'S QUESTION #6:

Data listings and electronic data sets will be provided for FDA analysis. Does the Agency concur?

FDA ANSWER:

- **Submission of the primary electronic data in MS Access is requested for the medical officer's review. A guidance to "Electronic Submission of Clinical Data" to DODP is attached.**

SPONSOR'S QUESTION #7:

Acceptance of the clinical information in a "rolling" fashion. Does the Agency concur?

- **Given the size of the application, we don't see much value in submitting the clinical information in a "rolling" fashion.**

Additional Medical Comment:

1. (b) (4)

Additional Discussion Points:

(b) (6)

FDA Question #1:

- (b) (6)

(b) (6)

FDA Question #2:

- (b) (6)

(b) (6)

FDA Comment:

- (b) (6)

Stable Disease Definition (Sequus):

Patient does not have progression and is stable for 2 months.

ACTION ITEM:

1. Sequus will provide the overheads presented at the meeting.

The meeting was concluded at 2:30pm. There were no unresolved issues or discussion points.

Debra M. Catterson 8/13/98
Debra Catterson, R.Ph.
Minutes Preparer

Concurrence Chair: Ivagani Chico 8/14/98
Ivagani Chico, M.D.
Medical Reviewer

cc: Original IND 36,778/NDA 50-718
HFD-150/Div Files
HFD-150/DPease
HFD-150/LVaccari
HFD-150/DCatterson/draft 7.13.98/ft. 8.13.98
HF-12/PDelaney

MEETING MINUTES