PRODUCT MONOGRAPH

MYOCET™

Doxorubicin Hydrochloride (Liposomes) for Injection

A chemotherapeutic agent containing:

Vial No. 1 Myocet™ Doxorubicin HCl for Injection, 50 mg/vial

Vial No. 2 Myocet™ Liposomes for Injection

Vial No. 3 Myocet™ Buffer for Injection

Therapeutic Classification:

Antineoplastic

Manufactured by:
Sopherion Therapeutics, Inc.
104 Carnegie Centre, Suite 200
Princeton, New Jersey, 08540
USA

Imported/Distributed by:
UPS SCS, Inc.
1453 Cornwall Road
Oakville, ON L6J7T5
Canada

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June 7, 2006

Control No. 101812

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(Logo)

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THERAPEUTIC CLASSIFICATION

Antineoplastic

WARNINGS: AS WITH ALL CHEMOTHERAPEUTIC AGENTS, MYOCET™ SHOULD BE ADMINISTERED ONLY UNDER THE SUPERVISION OF PHYSICIANS EXPERIENCED IN THE USE OF CANCER THERAPEUTIC AGENTS. MYOCET™ IS A LIPOSOMAL ENCAPSULATED FORM OF DOXORUBICIN HYDROCHLORIDE. CARDIOTOXICITY MAY OCCUR AS TOTAL LIFETIME CUMULATIVE DOSES OF DOXORUBICIN APPROACH 750 mg/m^2; PRIOR USE OF ANTHRACENES OR ANTHRACYCLINES, PRE-EXISTING CARDIAC CONDITIONS, OR MEDIASTINAL IRRADIATION MAY IMPACT CUMULATIVE DOSE LIMITS AND SHOULD BE TAKEN INTO ACCOUNT. IN ADDITION, THE KNOWN TOXICITIES OF DOXORUBICIN SUCH AS MYELOSUPPRESSION, ALOPECIA, GASTROINTESTINAL UPSET, ETC. HAVE ALSO BEEN REPORTED; THESE AND/OR IMPAIRED HEPATIC FUNCTION MAY IMPACT ACUTE DOSAGE LIMITS (i.e., DOSE ADMINISTERED PER CYCLE). DOSE REDUCTION MAY BE REQUIRED. OCCASIONAL ACUTE INFUSION REACTIONS HAVE BEEN DESCRIBED

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The active ingredient in Myocet™ is doxorubicin. Doxorubicin may exert its antitumor and toxic effects by a number of mechanisms, including inhibition of topoisomerase II, intercalation with DNA and RNA

polymerases, free radical formation and membrane binding. Clinical pharmacokinetic studies have shown that Myocet™ persists in the circulation, maintaining higher doxorubicin concentrations for longer periods than possible after equivalent doses of conventional doxorubicin. The enhanced therapeutic index of Myocet™ compared to conventional doxorubicin likely results from altered biodistributions, as shown in preclinical studies. In animals, Myocet™ reduced the distribution of doxorubicin to heart and gastrointestinal mucosa, but delivered doxorubicin effectively to tumors. Significant levels of doxorubicin administered as Myocet™ were maintained in human breast cancer xenografts, and accumulation of drug was more uniform and persistent than after administration of conventional doxorubicin. These data support the concept that liposomes can extravasate into tumors where blood vessel endothelia are often not completely intact, but do not extravasate into most normal tissues.

Pharmacokinetics

The plasma pharmacokinetics of doxorubicin and its metabolite, doxorubicinol, after the administration of a single, intravenous infusion (over 1 hour) of Myocet™ or conventional doxorubicin at a dose of 60 mg/m^2 (in combination with cyclophosphamide) were evaluated in 20 women (10 per treatment) with metastatic breast cancer. The pharmacokinetic parameters listed in Table 1 (obtained by noncompartmental methods) are for total plasma doxorubicin.

Table 1
Plasma Pharmacokinetics of Doxorubicin
After Single-Dose Administration
(Myocet™ or Conventional Doxorubicin (Dox) at
60 mg/m^2 Plus Cyclophosphamide at 600 mg/m^2)

			Myocet™				Dox			
			N	Mean	±	SD	N	Mean	±	SD
C_{max}[a]	Total doxorubicin	µM	9	16.0	±	9.3	9	1.7	±	0.3
$AUC_{(0-\infty)}$	Total doxorubicin	µM-h	10	79.3	±	69.6	9	3.9	±	0.4
Terminal T½	Total doxorubicin	H	10	16.4	±	5.4	10	42.9	±	8.6
Clearance	Total doxorubicin	L/h	10	5.1	±	4.8	9	46.7	±	9.6
Volume[b]	Total doxorubicin	L	10	56.6	±	61.5	9	1,451	±	258
C_{max}[a]	Doxorubicinol	µM	10	0.03	±	.01	10	0.04	±	0.02
T_{max}	Doxorubicinol	H	10	5.4	±	2.8	10	2.0	±	1.5
$AUC_{(0-\infty)}$	Doxorubicinol	µM-h	10	1.5	±	0.4	10	1.8	±	0.4
Terminal T½	Doxorubicinol	H	10	50.7	±	11.7	10	43.7	±	3.5

[a] Observed
[b] Volume of distribution at steady state

The plasma pharmacokinetics for total doxorubicin show relatively high inter-patient variability. In general, the plasma levels of total doxorubicin are substantially higher with Myocet™ than with conventional doxorubicin. The clearance of total doxorubicin after Myocet™ administration is lower (9-fold) and the volume of distribution at steady state is less (25-fold) than after conventional doxorubicin. Doxorubicinol (the major circulating metabolite of doxorubicin) appears in the plasma later with Myocet™ than with conventional doxorubicin.

The pharmacokinetics of Myocet™ have not been specifically studied in patients with renal or hepatic insufficiency. Doxorubicin is known to be eliminated in large part by the liver. Thus, the Myocet™ dosage may be reduced in patients with impaired hepatic function. (See PRECAUTIONS.)

INDICATION AND CLINICAL USE

Myocet ^{TM} is indicated for the first-line treatment of metastatic breast cancer in combination with cyclophosphamide.

CONTRAINDICATION

Myocet™ is contraindicated in patients with a history of hypersensitivity to doxorubicin or any of the other constituents of Myocet™.

WARNINGS

Cardiac Toxicity: Conventional doxorubicin and other anthracyclines can cause cardiotoxicity. The risk of that toxicity rises with increasing cumulative doses of those drugs, and is higher in individuals with a history of mediastinal irradiation or preexisting cardiac disease. Cardiotoxicity may manifest as an asymptomatic reduction in left ventricular ejection fraction (LVEF), symptomatic cardiomyopathy, or congestive heart failure (CHF). In the combined database of 542 patients with solid tumors treated with Myocet™ at starting doses less than 100 mg/m^2 , 16% of whom had received prior adjuvant doxorubicin up to 300 mg/m^2, the probability of developing CHF at various lifetime cumulative doses of doxorubicin (which could include both prior conventional doxorubicin and the doxorubicin in Myocet™) was estimated to be 1% at 600 mg/m^2, 3% at 700 mg/m^2, 5% at 750 mg/m^2, 11% at 800 mg/m^2, and 18% at 850 mg/m^2. Therefore, it is recommended that caution should be exercised if Myocet™ is to be dosed above a lifetime cumulative doxorubicin dose of 750 mg/m^2 ("cardiac threshhold dose"). This lifetime cumulative dose could be comprised of both conventional doxorubicin (up to 300 mg/m^2, per the clinical trial database), and Myocet™, or it could be exclusively Myocet™.

Cardiac function, particularly an assessment of left ventricular ejection fraction (LVEF) should be assessed before (i.e., at baseline), during (eg, after a lifetime cumulative doxorubicin dose of 300 mg/m^2 or more), or periodically as necessitated by a decrease in LVEF value, and after completion of therapy with Myocet™. Appropriate assessment modalities include MUGA scans and echocardiograms. Endomyocardial biopsies are sensitive indicators of myocardial damage, and may be performed at the discretion of the treating physician. Electrocardiograms (ECGs) may be considered before the start of

therapy with Myocet™, in order to ensure that there is no evidence of cardiac ischemia, hemodynamically unstable arrythmia, or recent myocardial infarction. Similarly, there should be no clinical signs or symptoms of unstable angina before starting therapy. Although Myocet™ does not cause cardiovascular insufficiency or unstable arrythmias, it is possible such conditions could worsen if a patient was treated with chemotherapy before these conditions resolved or prior to the initiation of appropriate medical interventions. In the absence of clinical symptomatology, ECGs are not indicated after therapy with Myocet™ in individuals with no evidence or history of myocardial ischemia or arrythmias prior to the beginning of therapy.

Although long-term or late cardiac toxicity due to Myocet™ is uncommon, it is reasonable to assess a patient for signs or symptoms of such toxicity by physical exam, MUGA or echocardiogram (with an ECG to rule out myocardial ischemia) after completion of Myocet™ therapy, especially if there is clinical evidence of possible cardiac insufficiency, such as exertional dyspnea or orthopnea at the following intervals: monthly for the first 3 months, and every 3 months thereafter until 12 months post therapy. Subsequently, such assessments may be performed on a bi-annual basis. This will ensure appropriate medical management if warranted, may prevent or lessen further damage due to strain, and could increase the likelihood of reversibility. Such cardiac function studies may also be considered prior to therapy with other potentially cardiotoxic agents (eg other anthracyclines or anthracenediones, the taxanes, or trastuzumab). (Also see 'Drug Interactions' section.)

Myelosuppression: Therapy with Myocet™ may cause myelosuppression. Careful hematologic monitoring (including white blood cell and platelet counts and hemoglobin) should be performed during therapy with Myocet™. Hematologic toxicity may require dose reductions or delays. Therapy with colony-stimulating factors may also be considered. Myocet™ should not be administered to individuals with absolute neutrophil counts (ANC) lower than 1,200 cells/μL or platelet counts less than 100,000/μL.

If a patient experiences grade 4 neutropenia (ANC <500 cells/μL) without fever lasting 7 days or more or grade 4 neutropenia of any duration with concurrent fever (≥38.5 C), consideration may be given to either adding filgrastim (G-CSF) or dose reduction (of both Myocet™ and cyclophosphamide) for all

subsequent cycles of therapy. If a patient experiences grade 4 thrombocytopenia or anemia, appropriate medical interventions (such as transfusion) should be taken, and therapy should be held until recovery to grade 2 toxicity levels. Thereafter, doses of both Myocet™ and cyclophosphamide should be reduced for all subsequent cycles of therapy, or consideration may be given to termination of therapy with Myocet™ and cyclophosphamide. (See 'Dose Reduction Guidelines' below.)

Dose Reduction Guidelines: Dose reduction may be considered for the hematologic toxicities described above, for grade 3 mucositis persisting 3 days or more, for grade 4 mucositis of any duration, or for grade 3 or 4 gastrointestinal toxicity that dose not respond to appropriate medical interventions and/or prophylaxis. Suggested dose reductions are as follows: if the initial Myocet™ dose was 60 mg/m^2, subsequent doses could be reduced to 50 mg/m^2, with a second dose reduction to 40 mg/m^2 if warranted by continuing unacceptable toxicity; if it were 75 mg/m^2, a reduced dose of 60 mg/m^2 could be administered, with further reductions as needed for subsequent cycles of therapy. If dose reduction is required, the dose of cyclophosphamide should initially be reduced by 100 mg/m^2 to 500 mg/m^2, with a possible additional dose reduction to 400 mg/m^2. Note that, prior to dose reduction for neutropenia, it may be reasonable to try prophylactic therapy with filgrastim (G-CSF) at 5 μg/kg/day subcutaneously beginning no sooner than 24 hours after the completion of both chemotherapy infusions and ending no less than 24 hours before the start of the next cycle of therapy, or when the ANC is >10,000 cells/μL .

Infusion Reactions: Occasional acute reactions associated with liposomal infusions have been reported. Reported symptoms have included flushing, dyspnea, fever, facial swelling, headache, back pain, chills, tightness in the chest and throat, and/or hypotension. These acute phenomena may be avoided by moderating or slowing the drug infusion rate. With the recommended one hour infusion of TLC D-99, the incidence of these symptoms were similar to those reported with conventional doxorubicin, and were reported in less than 10% of patients. Premedication is not required.

Carcinogenesis, Mutagenesis, and Fertility: Studies of carcinogenesis and mutagenesis have not been performed with Myocet™, but its parent compound, doxorubicin HCl, is known to be both mutagenic and carcinogenic. The effects of Myocet™ on fertility are not known.

Pregnancy: The safe use of the active ingredient of Myocet™, doxorubicin, has not been established in pregnancy. In some rodent species, doxorubicin has been shown to be embryotoxic, teratogenic, and abortifacient. Women of childbearing potential should therefore be advised to avoid pregnancy during therapy with Myocet™.

Nursing Mothers: Nursing mothers should be advised to discontinue nursing during Myocet™ therapy, as the potential effects on a nursing infant are unknown.

PRECAUTIONS

Allergies: Patients with a history of allergies to eggs or egg products should not be treated with Myocet™.

Pre-existing cardiac conditions: There are no studies of the safety or efficacy of Myocet™ in patients with baseline left ventricular ejection fraction below the lower limit of normal, a documented history of congestive heart failure, a myocardial infarction within 6 months of therapy, or a history of a hemodynamically unstable cardiac arrythmia. Therefore, the use of Myocet™ in patients with a history of any of these conditions cannot be recommended outside the setting of a clinical trial specifically designed to study these conditions.

Hepatic Impairment: As metabolism and excretion of Myocet™ occur primarily by the hepatobiliary route, evaluation of hepatobiliary function should be performed before and during therapy with Myocet™. Standard laboratory evaluations may be used to assess hepatobiliary function. Dose reduction of Myocet™ may be considered, based upon dosing recommendations for doxorubicin HCl, as follows: serum bilirubin 1.2-3.0 mg/dL = 50% dose reduction; serum bilirubin greater than 3.0 mg/dL = 75% dose reduction.

Drug Interactions: Specific drug compatibility studies have not been performed with Myocet™. Myocet™ may interact with drugs that are known to interact with the parent compound, conventional doxorubicin HCl. Such drugs include cyclosporine, phenobarbital, streptozocin, phenytoin, warfarin, and other drugs metabolized by the cytochrome P-450 system. Conventional doxorubicin HCl may also potentiate the toxicities of other antineoplastic agents, and is known to have pharmacokinetic interactions with paclitaxel. Concomitant therapy with other liposomal or lipid-complexed drugs or intravenous fat

emulsions could change the pharmacokinetic profile of Myocet™. Calcium channel blockers, which can be cardioactive and may interact with p-glycoprotein, or other such cardioactive agents may be administered cautiously with Myocet™. Combination therapy with other potentially cardiotoxic anticancer agents, such as the taxanes (paclitaxel and docetaxel) or trastuzumab is currently being studied in clinical trials, due to the potential for enhanced cardiotoxicity when such agents are given in combination regimens. Myocet™ should not be given concurrently with other anthracyclines or anthracenediones.

Special Populations and Pediatrics: Safety and efficacy of Myocet™ have been assessed in 124 patients (61 with Myocet™ and 63 with doxorubicin) age 65 and over utilizing data from two randomized studies versus conventional doxorubicin in metastatic breast cancer. The efficacy and cardiac safety of Myocet™ in this population were comparable to that observed in patients less than 65 years old. The safe and effective use of Myocet™ in pediatric oncology has not been established.

Injection Site Effects: Myocet™ should be considered an irritant and precautions should be taken to avoid extravasation. If extravasation occurs, the infusion should be immediately terminated. Ice may be applied to the affected area for approximately 30 minutes. Subsequently, the Myocet™ infusion should be restarted in a different vein than that in which the extravasation has occurred. Note that Myocet™ may be administered through a central or peripheral vein. In the clinical program, there were nine cases of accidental extravasation of Myocet™, none of which were associated with severe skin damage, ulceration, or necrosis.

In a comparative local tolerance study in rabbits, Myocet™ caused substantially less erythema and edema than conventional doxorubicin. Frank ulceration was observed in 1 of 3 rabbits after subcutaneous administration and 2 of 3 rabbits after perivenous administration of conventional doxorubicin. No ulcers were observed in rabbits given the same dose of Myocet™ by subcutaneous or perivenous injection.

Myocet™ may occasionally cause dizziness. Patients who experience this should not operate a vehicle.

ADVERSE REACTIONS

The safety database is composed of data from 1,066 patients, 716 of whom were treated with Myocet™. Data in Table 2 are based on the experience of 450 patients with metastatic breast cancer in two randomized Phase III trials of Myocet™/cyclophosphamide (CPA) combination therapy. In one combination trial, 296 patients were treated either with Myocet™/CPA (60/600 mg/m^2) (n=142) or doxorubicin/CPA (60/600 mg/m^2) (n=154) every 3 weeks; in the other trial, patients received either Myocet™/CPA (75/600 mg/m^2) (n=76) or epirubicin/CPA (75/600 mg/m^2) (n=78) every 3 weeks.

Table 2
Adverse Events
Studies in Combination With Cyclophosphamide

	Myocet™ + CPA 60 mg/m^2 (n=142)[a]	Dox + CPA 60 mg/m^2 (n =154)[a]	Myocet™ + CPA 75 mg/m^2 (n=76)[b]	Epi + CPA 75 mg/m^2 (n=78)[b]
Percent of Patients [Ref 2,4]	%	%	%	%
Hematologic[c]				
Neutropenia				
< 2,000/µL	97	97	100	99
< 500/µL	61	75	87	67
< 500/µL >7 days	1	5	26	31
Thrombocytopenia				
< 100,000/µL	51	47	54	27
< 20,000/µL	4	5	4	3
Anemia				
< 11 g/dL	88	92	96	78
< 8 g/dL	23	27	25	14
Infection				
All Grades	53	53	22	15
Grade 3 or 4	11	8	7	1
Neutropenic fever				
<500/µL, fever>38ºC	10	15	8	1
<500/µL, fever>38ºC[d]	9	13	5	1
Clinical				
Nausea/vomiting				
All Grades	80	84	84	81
Grade 3 or 4	13	16	21	19
Stomatitis/mucositis				
All Grades	40	56	36	12
Grade 3 or 4	4	7	7	0
Fatigue/malaise/asthenia				
All grades	42	47	33	31
Grade 3 or 4	6	5	0	1
Diarrhea				
All grades	28	38	21	19
Grade 3 or 4	3	8	1	1
Alopecia				
Pronounced	91	95	82	77
Cutaneous				
All grades	11	12	4	10
Injection site toxicity				
All grades	5	8	1	10

[a] From doxorubicin-controlled study; CPA at 600 mg/m^2
[b] From epirubicin-controlled study; CPA at 600 mg/m^2
[c] Regardless of causality
[d] With IV antibiotics or hospitalization
CPA, cyclophosphamide; Dox, conventional doxorubicin; Epi, epirubicin

The following grade 3/4 adverse events (possibly, probably, or definitely related to Myocet™) with an incidence of <5% were also observed (utilizing the database from 16 clinical studies in 647 patients with solid tumors). AIDS patients with Kaposi's sarcoma were not included.

Incidence less than 5% (grade 3 or 4, possibly, probably, or definitely related):

Body As a Whole: fever, rigors, hot flushes, pain, headache, dizziness,

dehydration, weight loss, sepsis

Cardiovascular: arrhythmia, chest pain, hypotension, pericardial effusion

Gastrointestinal: constipation, gastric ulcer, hepatic transaminases increased, alkaline phosphatase increased, serum bilirubin increased, jaundice

Hematologic: purpura, lymphopenia

Metabolic/Nutritional: hypokalemia, hyperglycemia

Musculoskeletal: back pain, muscle weakness, myalgia

Nervous System: gait abnormal, dysphonia

Psychiatric: anorexia, insomnia, agitation, somnolence

Respiratory: dyspnea, pharyngitis, epistaxis, pneumonitis, hemoptysis

***Skin and Appendages*:** nail disorder, injection site reaction, injection site infection, pruritus, folliculitis, herpes zoster, Rare (<1%), episodes of low grade radiation recall reactions have been reported.

Urogenital: oliguria, hemorrhagic cystitis

SYMPTOMS AND TREATMENT OF OVERDOSE

There is no potential for drug abuse with Myocet™. There is no known antidote for Myocet™ overdosage. The clinical picture to be expected with an overdose includes bone marrow suppression, severe mucositis, and cardiotoxicity, including CHF. Treatment of acute overdosage consists of hospitalization, antimicrobial therapy, platelet transfusions, and use of hematopoietic growth factors. Symptomatic treatment for severe mucositis is indicated. Symptomatic treatment for heart failure is indicated if CHF develops.

DOSAGE AND ADMINISTRATION

Myocet™ should be administered by infusion over 1 hour. Myocet™ should not be given as a bolus injection. The recommended initial dose of Myocet™ is 60 to 75 mg/m^2 in combination with cyclophosphamide (600 mg/m^2), administered every 3 weeks. Aseptic technique must be strictly observed throughout handling of Myocet™ since no bacteriostatic agent or preservative is present.

PHARMACEUTICAL INFORMATION

Drug Substance:

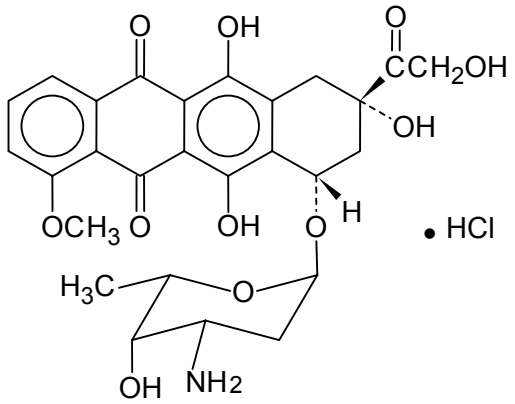
Proper Name:

Doxorubicin HCl

Chemical Name:

5,12-naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8, 11-trihydroxy-8-(hydroxylacetyl)-1-methoxy-, hydrochloride (8*s*-*cis*)-.

Structural Formula:



Molecular Weight:

579.99

Molecular Formula:

$C_{27}H_{29}NO_{11} \bullet HCl$

Description:

Doxorubicin HCl is a cytotoxic anthracycline antibiotic produced from a strain of *Streptomyces peucetius* var *caesius*. The hydrochloride salt is a red, free-flowing crystalline powder. Doxorubicin HCl is readily soluble in water, normal saline, methanol, acetonitrile and tetrahydrofuran, but only slightly soluble or insoluble in less polar organic solvents. A pKa of 8.22 was determined for the hydrochloride with N/20 sodium hydroxide. Doxorubicin HCl melts at 205 ° C with decomposition. Doxorubicin is stable in acidic solutions in the pH range 3.0 to 6.5.

Composition:

Myocet™ is a complex of doxorubicin-citrate encapsulated within the aqueous core of single lamellar liposomes that are composed of egg phosphatidylcholine:cholesterol (55:45 mole:mole). Encapsulation is achieved via an active loading process, which utilizes an inside acidic (pH ~4.5) proton concentration gradient. The internal complex is a flexible assembly of doxorubicin monomers stacked into fibers that are cross-linked by citrate into a hexagonal array with a 35 Å lattice repeat. After encapsulation of doxorubicin inside the liposomes, the drug to lipid ratio of Myocet™ is approximately 0.25:1 (wt:wt) and the pH is 6.5 to 8.5. Myocet™ is red-orange and opaque in appearance. All doses of Myocet™ refer to the doxorubicin HCl content delivered in the Myocet™ injections.

Contents of Single Use Vials:

Vial #1 Myocet™ Doxorubicin HCI for Injection

Doxorubicin HCI, USP	50 mg
Lactose,NF (hydrous)	250 mg

Vial #2 Myocet™ Liposomes for Injection

Egg Phosphatidylcholine	142.6mg
Cholesterol, NF	57.4 mg
Citrate Buffer (57.6 mg/mL) q.s.	2mL

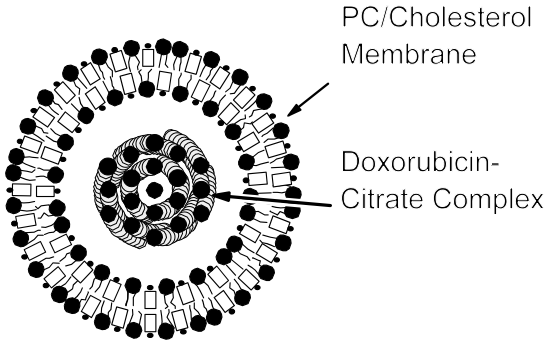
Vial #3 Myocet™ Buffer for Injection

Sodium Carbonate anhydrous, NF	54.6 mg
Water for Injection, USP q.s.	3.1 mL

Each prepared vial of Myocet™ contains 50 mg of doxorubicin HCl, and each milliliter of Myocet™ contains:

Doxorubicin HCl	2.0 mg
Egg phosphatidylcholine	5.4 mg
Cholesterol	2.2 mg
Citric acid, monohydrate	4.4 mg
Sodium carbonate	2.2 mg
Lactose	10.0 mg
Sodium Chloride Injection	7.2 mg

Myocet™

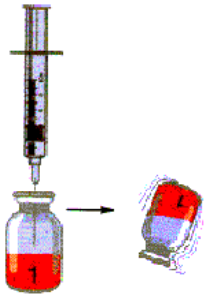


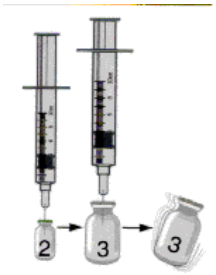
Stability and Storage Recommendations:

The Myocet™ carton should be stored in the refrigerator (2 to 8 °C) until time of use. Do not freeze. Single use vials. Discard unused portion.

Reconstituted Solution:

Preparation for Administration:

STEP 1. SET UP • Turn on water bath and allow water to equilibrate at 58 °C (55 to 60 °C). • Remove Myocet™ (Liposomal Doxorubicin Injection) carton from the refrigerator.	
STEP 2. RECONSTITUTE Myocet™ DOXORUBICIN HCl FOR INJECTION, USP (vial No.1) • Withdraw 20 mL sodium chloride injection (0.9%) and inject into each 50-mg vial of Myocet™ Doxorubicin HCl for Injection, USP intended for preparation (vial No.1). • Shake well in the inverted position to ensure doxorubicin is fully dissolved.	
STEP 3. HEAT IN WATER BATH • Heat the Myocet™ Doxorubicin HCl for Injection, USP (vial No.1) in a water bath (55 to 60 °C) for 10 minutes (not to exceed 15 minutes). • While heating, proceed to Step 4.	

STEP 4. ADJUST pH OF LIPOSOMES • Withdraw 1.9 mL of Myocet™ Liposomes for Injection (vial No. 2). • Inject into Myocet™ Buffer for Injection (vial No. 3). *Pressure buildup may require venting.* • Shake well.	
STEP 5. ADD LIPOSOMES TO DOXORUBICIN • Using syringe, withdraw the entire vial contents of pH-adjusted liposomes (vial No. 3). • Remove Myocet™ Doxorubicin HCl for Injection, USP (vial No.1) from the water bath. SHAKE VIGOROUSLY. Then IMMEDIATELY (within 2 minutes) inject pH- adjusted liposomes into vial of heated 50 mg Myocet™ Doxorubicin HCl for Injection, USP (vial No.1). • SHAKE VIGOROUSLY. • WAIT FOR A MINIMUM OF 10 MINUTES BEFORE USING.	

Parenteral Product:

The constituted Myocet™ Liposome Injection, 2 mg/mL may be:

a. Infused piggyback into a running IV line of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

b. Diluted in either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a concentration greater than or equal to 0.04 mg/mL doxorubicin (eg, maximum 50 × dilution), before infusion.

Myocet™ must not be given by the intramuscular or subcutaneous route.

Once constituted, Myocet™ Liposome Injection should be a red-orange, opaque, homogeneous dispersion. As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used. Discard unused portion. Do not use the preparation if foreign particulate matter is present. Do not mix with other drugs.

Store constituted Myocet™ for administration at room temperature for up to 8 hours or in a refrigerator (2 to 8 °C) for up to 72 hours. Do not freeze.

AVAILABILITY OF DOSAGE FORMS

Myocet™ is a chemotherapeutic agent containing:

Vial No. 1. Myocet™ Doxorubicin HCl for Injection, 50 mg/vial

Vial No. 2. Myocet™ Liposomes for Injection

Vial No. 3. Myocet™ Buffer for Injection

INFORMATION FOR THE PATIENT

What is Myocet™ and how does it work?

Myocet™ is a drug that is used to treat patients who have breast cancer that has spread to other parts of the body. It is a safer form of a drug called doxorubicin. Doxorubicin, given in its standard form, is a very effective treatment for many cancer patients but it can cause severe side effects. These side effects include permanent damage to the heart, problems with the lining of the stomach, and low white blood cell counts. Myocet™ has been designed to help lessen some of the severe side effects that can occur when patients are given doxorubicin.

Myocet™ reduces side effects by trapping the active ingredient, doxorubicin, inside tiny sacs called liposomes. Liposome encapsulated doxorubicin is less likely to reach certain healthy tissues (such as the heart and gastrointestinal mucosa) and may accumulate and persist longer in cancer tissue than conventional doxorubicin. Therefore, Myocet™ delivers doxorubicin treatment directly to tumors with less damage to other parts of the body.

How is Myocet™ given and how often will I be treated?

Myocet™ is injected into a vein over a 1-hour period. Treatment with Myocet™ is usually repeated every 3 weeks; however, your doctor will determine how often you should receive treatment based on your individual needs.

Do I need to do anything before being treated with Myocet™?

You do not need to take any medication before being treated with Myocet™.

Will my heart be protected if I am treated with Myocet™?

Because Myocet™ is a form of doxorubicin, heart damage is still a possibility over the long term. Your doctor will monitor you carefully to find out if your heart is being affected by treatment. Most likely, your heart will be able to tolerate more doxorubicin if you are treated with Myocet™ .

What side effects may I get when I receive Myocet™ treatment?

Although patients who are treated with Myocet™ generally get fewer side effects, you may experience the following:

Low Blood Cell Counts: Many drugs used to treat cancer affect the bone marrow, where blood cells are made. During treatment with Myocet™, the number of white blood cells, red blood cells, or platelets circulating in your blood may decrease. Your doctor will give you blood tests to find out if this is occurring, and may possibly treat you with medications that reverse this side effect.

Reaction to Administration of Myocet™: When Myocet™ is injected into your vein, you may feel flushed or feverish or experience chills. This occurs only occasionally and can be treated by giving you the drug over a longer period.

Hair Loss: You may lose some or all of the hair on your head, as well as on other parts of your body. When treatment is over, the hair will grow back. If you lose your hair, you may want to wear a wig or other head covering. Your doctor or nurse can advise you where to purchase these items.

*Tiredness***:** Tiredness, weakness, and fatigue are common in patients who are being treated for cancer. Sometimes this is because of low red blood cell counts, which can be corrected. Your doctor or nurse can also help you with diet, exercise, and other strategies to overcome these feelings.

Do no drive or participate in activities that require alertness if you are drowsy, dizzy or lightheaded.

Nausea/Vomiting/Diarrhea: Nausea, vomiting, and diarrhea are common side effects of cancer chemotherapy and may occur with Myocet™. However, it is important to know that these side effects can often be prevented or substantially reduced with simple medications. Make sure you let your doctor know if you experience any of these side effects so he or she can give you the appropriate treatment.

The side effects listed above are the most common ones experienced by patients who have received Myocet™. If you experience any other unusual or troublesome effects, report them to your doctor immediately.

Who should not be treated with Myocet™?

Myocet™ should not be administered to patients who have had a reaction to standard doxorubicin, women who are pregnant or nursing a baby, and people who are allergic to eggs or egg products.

What other drugs should be avoided while being treated with Myocet™?

The following drugs are known to interact with Myocet™: cyclosporine, phenobarbital, streptozocin, phenytoin, warfarin, and all other medications including those obtained without prescription. Please advise your doctor if you are taking any of these medications.

For additional information about Myocet™, talk to your doctor—or you may call 1-800-335-5476. For complete Myocet™ prescribing information, refer to the product monograph.

PHARMACOLOGY

Animal Pharmacology:

The active ingredient of liposomal doxorubicin injection is doxorubicin HCl. Encapsulation of doxorubicin in liposomes is not believed to change its intrinsic mechanism of action or its spectrum of activity.

In four well-controlled, murine tumor models, liposomal doxorubicin injection showed antitumor activity at least equivalent to that observed with conventional doxorubicin (Table 3). Because liposomal doxorubicin injection is less toxic than conventional doxorubicin, higher doses could be administered, resulting in greater therapeutic effects in these models. In the M5076 model, liposomal doxorubicin injection produced superior increases in life span compared to equivalent doses of conventional doxorubicin.

Table 3
Antitumor Activity of Liposomal Doxorubicin HCl in Murine Tumor Models

MODEL		ANTITUMOR POTENCY	OPTIMAL DOSE		MAXIMUM THERAPEUTIC EFFECT
			FREE DOX	TLC D-99	
L1210	(ascites)	TLC D-99 = FREE DOX	15	27	TLC D-99 > FREE DOX
P388	(ascites)	TLC D-99 = FREE DOX	15	27	TLC D-99 > FREE DOX
M5076	(sc solid tumor)	TLC D-99 > FREE DOX	6.7	10	TLC D-99 > FREE DOX
B16	(sc solid tumor)	TLC D-99 = FREE DOX	6.7	10	TLC D-99 > FREE DOX

There is currently no animal or in vitro evidence that liposomal doxorubicin injection confers any advantage over conventional drug in doxorubicin-resistant tumors on a weight-for-weight basis. The ability to give higher doses (due to less toxicity) may be effective in resistant tumors, but this has not been assessed.

Human Pharmacology:

Pharmacokinetics

The plasma pharmacokinetics of doxorubicin and its metabolite, doxorubicinol, after the administration of a single, intravenous infusion (over 1 hour) of Myocet™ or conventional doxorubicin at a dose of 60 mg/m^2 (in combination with cyclophosphamide) were evaluated in 20 women (10 per treatment) with metastatic breast cancer. The pharmacokinetic parameters listed in Table 4 (obtained by noncompartmental methods) are for total plasma doxorubicin.

Table 4
Plasma Pharmacokinetics of Doxorubicin
After Single-Dose Administration
(Myocet™ or Conventional Doxorubicin (Dox) at 60 mg/m^2 Plus Cyclophosphamide at 600 mg/m^2)

			Myocet™				Dox			
			N	Mean	±	SD	N	Mean	±	SD
C_{max}[a]	Total doxorubicin	µM	9	16.0	±	9.3	9	1.7	±	0.3
$AUC_{(0-\infty)}$	Total doxorubicin	µM-h	10	79.3	±	69.6	9	3.9	±	0.4
Terminal T½	Total doxorubicin	H	10	16.4	±	5.4	10	42.9	±	8.6
Clearance	Total doxorubicin	L/h	10	5.1	±	4.8	9	46.7	±	9.6
Volume[b]	Total doxorubicin	L	10	56.6	±	61.5	9	1,451	±	258
C_{max}[a]	Doxorubicinol	µM	10	0.03	±	.01	10	0.04	±	0.02
T_{max}	Doxorubicinol	H	10	5.4	±	2.8	10	2.0	±	1.5
$AUC_{(0-\infty)}$	Doxorubicinol	µM-h	10	1.5	±	0.4	10	1.8	±	0.4
Terminal T½	Doxorubicinol	H	10	50.7	±	11.7	10	43.7	±	3.5

[a] Observed

[b] Volume of distribution at steady state

The plasma pharmacokinetics for total doxorubicin show relatively high inter-patient variability. In general, however, the plasma levels of total doxorubicin are substantially higher with Myocet™ than with conventional doxorubicin. The clearance of total doxorubicin after Myocet™ administration is lower (9-fold) and the volume of distribution at steady state is less (25-fold) than after conventional doxorubicin. Doxorubicinol (the major circulating metabolite of doxorubicin) appears in the plasma later with Myocet™ than with conventional doxorubicin.

The pharmacokinetics of Myocet™ have not been specifically studied in patients with renal or hepatic insufficiency. Doxorubicin is known to be eliminated in large part by the liver. Thus, the Myocet™ dosage may be reduced in patients with impaired hepatic function. (See PRECAUTIONS.)

Clinical Studies:

Metastatic Breast Cancer: Data from three randomized, active-controlled, Phase III clinical trials support the use of Myocet™ for the first-line treatment of metastatic breast cancer. Two of these trials studied Myocet™ in combination with cyclophosphamide (CPA) (controls were doxorubicin/CPA in one study; epirubicin/CPA in the other). The third trial studied single-agent therapy with Myocet™ versus conventional doxorubicin.

Table 5
Summary Efficacy Results:
Combination Regimens (Study 1 and Study 3) with Cyclophosphamide

	Study 1 Combination		Study 3 Combination	
Treatment Arm (Dose mg/m²)	**Myocet™ (60) + CPA (600)**	**Doxorubicin (60) + CPA (600)**	**Myocet™ (75) + CPA(600)**	**Epirubicin (75) + CPA (600)**
Patients (N)	142	155	80	80
Total	297		160	
Antitumor efficacy				
Response[a,b]				
Rate	43%	43%	46%	39%
95% CI (%)	(35-52)	(35-51)	(35-58)	(28-50)
Rel risk (Myocet™: doxorubicin or epirubicin (95% CI)	1.01 (0.78-1.31)		1.19 (0.83-1.72)	
Progression-free survival				
Median (months)	5.1	5.5	7.7	5.6
No prior doxorubicin	5.1	5.9	--	--
Prior doxorubicin treatment	7.2	2.5	--	--
95% CI (%)	--	--	(5.4-8.9)	(4.4-6.4)
Rel risk (doxorubicin or epirubicin:Myocet™)	1.03		1.522	
Log-rank *P*-value[c]	0.821		0.022	
Time to treatment failure				
Median (months)	4.6	4.4	5.7	4.4
No prior doxorubicin	4.6	4.6	--	--
Prior doxorubicin treatment	4.6	2.1	--	--
95% CI (%)	--	--	(4.2-8.2)	(3.1-5.6)
Rel. risk (doxorubicin or epirubicin:Myocet™)	1.139		1.637	
Log-rank *P*-value[c]	0.314		0.007	
Survival				
Median (months)	18.6	16.4	18.3	16.0
No prior doxorubicin	18.6	16.5	--	--
Prior doxorubicin treatment	>44.1	14.6	--	--
95% CI (%)	--	--	(14.9-23.8)	(12.8-18.3)
Rel risk (doxorubicin or epirubicin:Myocet™)	1.042		1.147	
Log-rank *P*-value[c]	0.793		0.504	

[a] Protocol-specified test of noninferiority in efficacy: one-sided test to rule out 15% difference. P-value (15% delta): Study 1 - 0.002, Study 3 - 0.0019

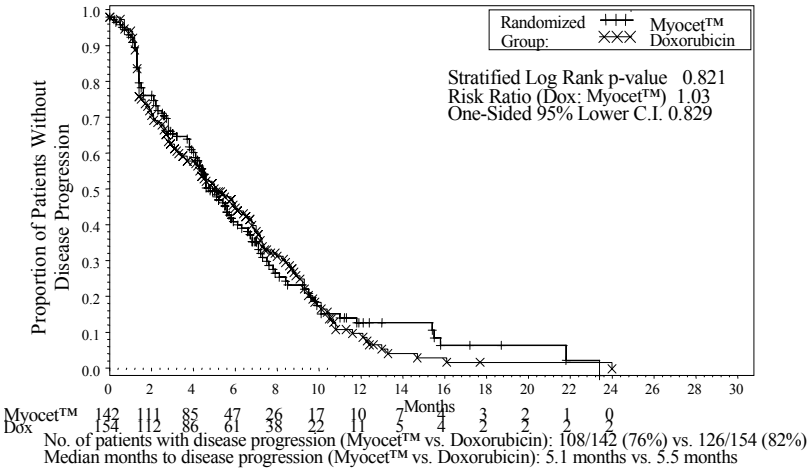
[b] Test of noninferiority in efficacy: one-sided test to rule out 10% difference. P-value (10% delta): Study 1 - 0.03, Study 3 - 0.0123

[c] Two-sided test for null hypothesis of no difference.

Myocet™ plus CPA versus doxorubicin plus CPA (**Combination Study 1**): This study was conducted in 297 patients with no prior treatment with cytotoxic agents for metastatic breast cancer. Myocet™ or doxorubicin 60 mg/m^2 plus CPA 600 mg/m^2 was administered every 21 days. Baseline characteristics were similar for both groups except that a higher proportion of patients in the Myocet™ group had visceral involvement (72% versus 61%), which was not statistically significant. Ten percent (10%) in each group had received prior doxorubicin.

In this pivotal study, the results fulfilled the protocol-defined criteria of significant reduction in cardiotoxicity (p = 0.0001, two-sided, log-rank test) and noninferiority in efficacy (Table 5), as assessed by response rates (p= 0.002, one-sided test, to rule out a 15% delta). Overall response rates were 43% in both treatment groups (hazard ratio Myocet™:doxorubicin 1.02). Disease progression was observed for 76% of Myocet™ patients versus 82% of conventional doxorubicin patients. There was no difference between the two treatment groups in progression-free survival (*p*=0.821), with a median progression-free survival of 5.1 months in patients on Myocet™/cyclophosphamide versus 5.5 months in those who received doxorubicin/cyclophosphamide (Table 5 and Figure 1). There was also no difference in median survival between the two groups, which was 18.6 months in the Myocet™ patients and 16.4 months on the active-control arm (*p*=0.793) (Table 5).

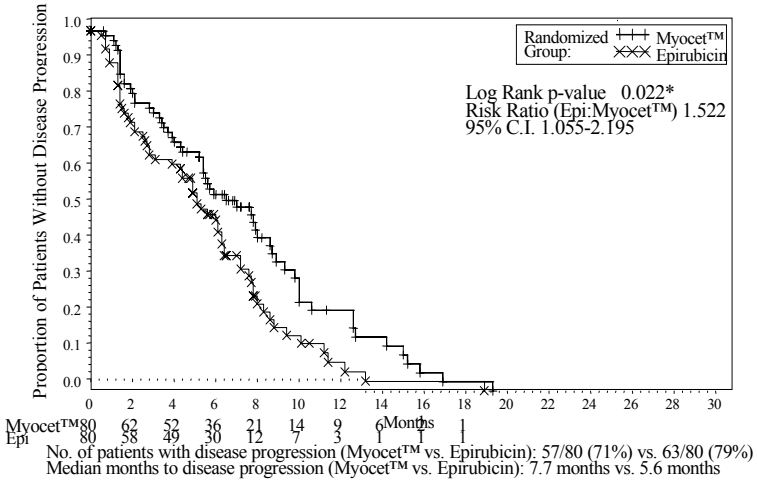
Figure 1
Progression-Free Survival
Intent-to-Treat Population
(Combination Study 1)



Myocet™ versus epirubicin (**Supportive Combination Study 3**): Results from the combination study are substantiated by results from another randomized comparative study of Myocet™ or epirubicin 75 mg/m^2 plus CPA 600 mg/m^2 administered every 21 days in 160 patients with metastatic breast cancer (Table 5 and Figure 2). No prior anthracycline was allowed in this study. The response rate in Myocet™-treated patients was 46% versus 39% for patients who received epirubicin.

In this supportive combination study, disease progression was observed in 71% of Myocet™ patients versus 79% of epirubicin patients. As demonstrated in Figure 2, the Myocet™ group had longer progression-free survival (7.7 months) versus the epirubicin group (5.6 months) (p=0.022).

Figure 2
Progression-Free Survival
Intent-to-Treat Population
(Supportive Combination Study 3)



Myocet™ versus doxorubicin (**Single-agent Study 2**): A single-agent, controlled, randomized study was conducted in 224 patients with no prior treatment with cytotoxic agents for metastatic breast cancer. Myocet™ or doxorubicin 75 mg/m^2 was administered every 21 days with a dose titration of ± 15 mg/m^2 up to a maximum of 105 mg/m^2. In this study, seventeen percent (17%) of Myocet™ patients versus 18% of doxorubicin patients had received prior doxorubicin therapy. An equal proportion of patients had visceral involvement in each group (72%).

Overall responses on both arms of the study were 26%, (hazard ratio Myocet™:doxorubicin 0.99).

A significant difference in median survival favoring the doxorubicin arm was observed in a subset of patients (58% of those on Myocet™ and 57% of those on doxorubicin) who did not have hepatic metastases (p=0.03). This subset also had significant differences favoring the doxorubicin arm in hormone receptor positivity (progesterone receptor positivity, p=0.03 and estrogen receptor positivity, p=0.05). There was no significant difference in progression-free survival in this subset of patients without hepatic metastases *(*p=0.21).

In the contrasting subset of patients with hepatic metastases, there was no difference in prognostic factors (such as hormone receptor positivity), and no difference in median survival (p=0.979) or progression-free survival (p=0.663).

In the overall group, a significant difference (p=0.02) in the prognostic factor of progesterone receptor positivity was observed, which favored the doxorubicin arm, and there was a difference in median survival favoring the doxorubicin patients that did not reach statistical significance (p=0.08), but no difference between the two groups in progression-free survival (p=0.43).

Cardiotoxicity:

Resting MUGA scans were performed in the doxorubicin-controlled combination study (Study 1) and the single-agent study (Study 2) only to measure LVEF. All MUGA scans were sent to a core laboratory at Yale University Cardiology Center for interpretation and read prospectively by a designated cardiologist blinded to study treatment. The parameters by which cardiac events were assessed include:

1. Development of clinical CHF.
2. Decrease in LVEF by ≥10 points from baseline to a final value of < 50% (type II).
3. Decrease in LVEF by ≥20 points from baseline value to a final value of ≥ 50% (type I).
4. In the single-agent study (Study 2) only, an endomyocardial biopsy result of grade ≥2.5. Endomyocardial biopsies were not performed in Study 1.

Analysis of cardiotoxicity showed a statistically and clinically significant reduction in cardiac events in the Myocet™-treated patients. The proportion of patients developing a cardiac event was significantly less with Myocet™, and the cardiac events developed at a significantly higher cumulative dose and later time when patients were treated with Myocet™.

In the combination study (Study 1), 9 patients in the Myocet™ group versus 32 patients in the doxorubicin group had a decrease in LVEF ≥ 10% to < 50% from baseline. No Myocet™ patients versus 5 doxorubicin patients developed CHF.

In the single-agent study (Study 2), 14 patients in the Myocet™ group versus 33 patients in the doxorubicin group had a decrease in LVEF ≥10% and <50% from baseline. Two patients (2%) in the Myocet™ group versus 9 doxorubicin patients (8%) developed CHF. Table 6 summarizes the reduction in cardiotoxicity in both studies.

Note that in the supportive combination Study 3 (the epirubicin controlled study), cardiac function was assessed by echocardiography rather than by MUGA scans. Therefore, Study 3 is not included in this analysis.

Table 6
Summary of Reduction in Cardiotoxicity

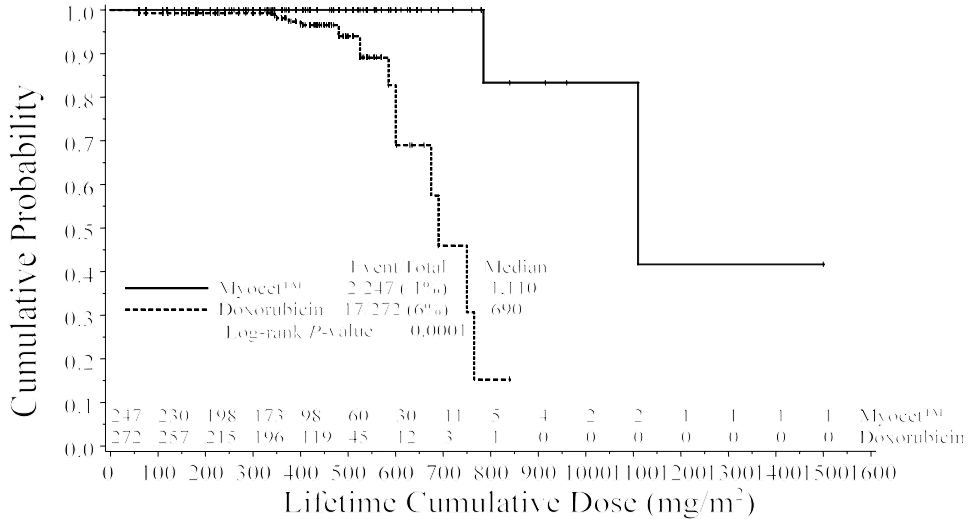
	Combination Study 1		**Single-agent Study 2**	
Treatment Arm:	Myocet™+ CPA	Dox+CPA	Myocet™	Dox
Cardiac events				
LVEF change (type I, II)	9	32	14	33
Cardiac biopsy ≥2.5	--	--	5	12
CHF	0	5	2	9
Median lifetime cum dose (mg/m^2) to cardiac event	> 1,800	480	785	532.5
Log-rank *P*-value[a]	0.0001		0.0001	
Median time since first dose of study drug to cardiac event	>15.2 mo	9.8 mo	9.8 mo	6.9 mo
Log-rank *P*-value[a]	0.0005		0.0007	
CHF by lifetime cum dose (mg/m^2) of doxorubicin	> 1,920	> 660	1,100	690
Log-rank *P*-value[a]	0.0206		0.0001	

[a]Two-sided test for null hypothesis of no difference.

Results of endomyocardial biopsy data from 36 patients were also obtained in the single-agent study (Study 2). All biopsies were sent to a core pathologist (Stanford University) for grading according to the Billingham scale on a treatment-blinded basis. Five patients (26%) in the Myocet™ group had a biopsy grade of 2.5 (moderate to severe myocardial damage) and none had a biopsy grade of 3 (severe), compared with 5 (29%) and 7 (41%), respectively, in the doxorubicin group.

LVEF <30% is an objective measure of severe cardiotoxicity that is highly correlated with the development of CHF. The lifetime cumulative dose to onset of clinical CHF or LVEF < 30% in the combination study and single-agent study are presented in Figure 3.

Figure 3
Combination (Study 1) and Single-Agent (Study 2) Studies:
Total Lifetime Dose of Doxorubicin to
Clinical CHF and/or LVEF < 30%



TOXICOLOGY

The toxicology of liposomal doxorubicin injection has been studied primarily in dogs, with selected studies in mice and rabbits. In general, toxicities found with liposomal doxorubicin injection are qualitatively similar to those found with conventional doxorubicin. The most important chronic toxicity of conventional doxorubicin in the dog, and in humans, is cardiomyopathy. Liposomal doxorubicin injection also causes cardiotoxicity, but at significantly higher cumulative doses. Following is a summary of key findings in the toxicology studies.

Acute Toxicities: Liposomal doxorubicin injection was less acutely toxic than conventional doxorubicin in the mouse as evidenced by a 50% lethal dose of 32 mg/kg for liposomal doxorubicin injection versus 17.5 mg/kg for conventional doxorubicin after a single bolus, intravenous dose. The time to death (3 to 5 days) was similar in both treatment groups, suggesting a common cause of death for the two agents.

A transient (several hours) increase in body temperature occurring within 24 hours of treatment was an adverse effect found in dogs and rabbits treated with liposomal doxorubicin injection but not in animals treated with conventional doxorubicin or empty liposomes. The highest temperature recorded in dogs was 105.6 ˚F (normal temperature is ~ 102 ˚F). The cause of this pyrexia is unknown.

The **hemolymphoproliferative system** was affected by both liposomal doxorubicin injection and conventional doxorubicin in all studies conducted in dogs. (Liposomal doxorubicin injection also caused bone marrow atrophy in rabbits in a single-dose study.) Peripheral white blood cell counts (primarily neutrophils, but also lymphocytes) and platelets decreased in a dose-dependent manner in dogs receiving single or repeated intravenous doses of liposomal doxorubicin injection or conventional doxorubicin on about day 7 post-dose and recovered within 2 to 3 weeks. There was no clear difference in the time or extent of myelosuppression or time to recovery after administration of the two formulations. Bone marrow atrophy (assessed histologically) was similar or slightly more severe with liposomal doxorubicin injection compared with conventional doxorubicin.

The incidence and severity of atrophy of the lymphoid organs (thymus, lymph nodes, spleen) was similar between liposomal doxorubicin injection and conventional doxorubicin in all studies in dogs.

Testicular atrophy (accompanied by epididymal aspermia) is often noted in dogs treated with single or repeated doses of doxorubicin. The incidence and severity of testicular atrophy were similar in dogs treated with liposomal doxorubicin injection and conventional doxorubicin.

Dogs are known to be particularly sensitive to the **gastrointestinal effects** of anthracyclines, and acute gastrointestinal signs were noted in dogs that received liposomal doxorubicin injection or conventional doxorubicin in preclinical studies. Quantitative but not qualitative differences were seen in the severity and frequency of gastrointestinal signs in dogs receiving liposomal doxorubicin injection compared with those receiving conventional doxorubicin. Emesis, decreased food consumption, loose stools, diarrhea, and bloody diarrhea were seen within the first week after each cycle of dosing in many dogs receiving either formulation. In general, dogs receiving 1.5 mg/kg of liposomal doxorubicin injection once every 3 weeks showed only mild signs of GI toxicity. In the single-dose, 5 daily dose, and 8-cycle studies, it appeared that liposomal doxorubicin injection caused less GI disturbance than conventional doxorubicin at similar doses.

Alopecia and/or hyperpigmentation occurs with conventional doxorubicin treatment in rodents and dogs and occurred in both of the long-term (8-cycle and 8- to 12-cycle) studies in dogs reported here. In the 8-cycle study, alopecia was noted in all dogs receiving conventional doxorubicin but in none of those receiving liposomal doxorubicin injection. In the 8- to 12-cycle study, hyperpigmentation of the skin was noted in all dogs receiving conventional doxorubicin or liposomal doxorubicin injection at 1.5 mg/kg. Hair loss occurred in most dogs also, although this may have been less severe in animals receiving liposomal doxorubicin injection. Thus, the incidence and severity of alopecia with repeated cycles of liposomal doxorubicin injection appear to be the same or slightly less than that seen with the same dose of conventional doxorubicin.

Doxorubicin is known to cause ulceration when extravasation from the injection site occurs.There were no instances of severe injection site reactions in any of the intravenous single- or repeated-dose studies with liposomal doxorubicin injection. In a comparative **local tolerance** study in rabbits, liposomal doxorubicin injection caused substantially less erythema and edema than conventional doxorubicin. Frank ulceration was observed in 1 of 3 rabbits after subcutaneous administration and 2 of 3 rabbits after perivenous administration of conventional doxorubicin. No ulcers were observed in rabbits given the same or twice the volume of liposomal doxorubicin injection by perivenous or subcutaneous injection.

Dermal toxicity (palmar-plantar erythrodysesthesias, or "hand-and-foot syndrome") is occasionally seen in patients receiving prolonged infusions of conventional doxorubicin and is the dose intensity-limiting toxicity with Stealth™-type liposomal formulations of doxorubicin. This cutaneous lesion occurred in rats, rabbits, and dogs in the preclinical toxicology studies with Stealth™ liposomal doxorubicin. Palmar-plantar erythrodysesthesias were not observed in any animal treated with liposomal doxorubicin injection.

Cardiomyopathy induced by the anthracyclines is considered one of the most severe toxicities and is often the cumulative dose-limiting toxicity. It is a progressive, irreversible lesion that can lead to heart failure and death. Cardiomyopathy has been induced by doxorubicin in all species in which it has been investigated, including mouse, rat, rabbit, dog, monkey, and pig, and closely resembles that seen in humans. The predominant light microscopic change is a multifocal vacuolar degeneration of cardiac myofibers. These lesions are more prevalent in the left ventricular wall and in the septum.

Two comparative studies in dogs demonstrated that liposomal doxorubicin injection is less cardiotoxic than the same cumulative dose of conventional doxorubicin. In the first study, dogs received 1.5 mg/kg of either liposomal doxorubicin injection or conventional doxorubicin intravenously once every 3 weeks for 8 cycles (cumulative dose = 12 mg/kg or ~240 mg/m^2). At the end of the treatment period (157 to 164 days), all six animals in the conventional doxorubicin group had histologic evidence of cardiotoxicity (moderate to severe vacuolization of cardiac muscle fibers) whereas none of the six dogs that had received liposomal doxorubicin injection showed macroscopic or microscopic changes in the heart.

A second study was conducted to evaluate a longer duration of treatment with a higher cumulative dose. Dogs received 1.5 mg/kg liposomal doxorubicin injection or conventional doxorubicin once every 3 weeks for up to 12 cycles (cumulative dose = 18 mg/kg or ~360 mg/m^2). There were five dogs per sex in each treatment group, two per sex scheduled for necropsy after 8 cycles and three per sex scheduled for necropsy after 12 cycles. (Additional groups of dogs received saline, empty liposomes, or 2.25 mg/kg liposomal doxorubicin injection.) None of the dogs in the conventional doxorubicin group survived the full 12-cycle treatment whereas all of the animals in the liposomal doxorubicin injection group survived until their scheduled necropsy. After 8 cycles of treatment, all animals treated with conventional doxorubicin (except one female, which died of pneumonia after a single cycle) had lesions of myocardial degeneration consistent with doxorubicin toxicity. Most of the animals treated with liposomal

doxorubicin injection for 8 cycles also had microscopic lesions of doxorubicin-induced toxicity, but at a substantially reduced severity compare to those treated with conventional doxorubicin. The myocardial degeneration seen in liposomal doxorubicin injection animals after 12 cycles was generally equal to or less severe than that seen with conventional doxorubicin after 8 cycles.

Reproduction: There have been no studies of the effect of Myocet™ on reproduction in animals or humans, but there is data in animals on the active component of Myocet™, doxorubicin. Doxorubicin and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models. It is embryotoxic and teratogenic in rats, and embryotoxic and abortifacient in rabbits. Therefore, women of childbearing potential should be advised to avoid doxirubicin during pregnancy. If doxorubicin is to be used during pregnancy, the patient should be advised of potential hazard to the fetus. Lactating women should be advised not to breast-feed during therapy with doxorubicin. Formal fertility studies have not been done, but doxorubicin is known to cause testicular atrophy in rats and dogs.

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