I. ANNOTATED PACKAGE INSERT

A. Introduction

The drug product that is the subject of this NDA is called DOX-SL Injection. "DOXIL" is an early name for the product and is used synonomously with DOX-SL throughout this document.

The following section presents the proposed text of the DOX-SL labeling. The annotations that appear to the right of the text refer to sections in this NDA of literature references. The literature references cited in the text of the labeling are listed in subsection M below. For the remainder of this Overall NDA Summary, a list of reference citations is presented in Section X.

DOX-SL™
(pegylated liposomal doxorubicin HCl) Injection
FOR INTRAVENOUS USE ONLY

Rx

A Product of Liposome Technology, Inc.

WARNINGS

1. Experience with DOX-SL™ is limited in evaluating cardiac risk. Therefore warnings related to use of doxorubicin HCl, USP should be observed.

With doxorubicin HCl, USP serious irreversible myocardial toxicity with delayed congestive failure often unresponsive to any cardiac supportive therapy may be encountered as total dosage of doxorubicin in any formulation approaches 550 mg/m^2. Caution should be observed in patients who have received other anthracyclines.

This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy.

Until more information is known, cardiac function should be carefully monitored in patients treated with DOX-SL.

Patients with a history of cardiovascular disease should be administered DOX-SL only when the benefit outweighs the risk to the patient.

2. Severe myelosuppression may occur.

3. DOX-SL should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

ADRIAMYCIN PFS™ Package Labeling. In: *Physician's Desk Reference®*. 47th ed. Montvale, NJ: Medical Economics Data;1993: 560 - 561.

DESCRIPTION

DOX-SL™ is doxorubicin hydrochloride (HCl) encapsulated in Stealth® liposomes for intravenous (IV) administration.

The active ingredient of DOX-SL is doxorubicin HCl, USP; a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius*. Vol. 1.2, Page 23

DOX-SL is provided as a sterile, translucent, red suspension in 10-mL glass, single use vials. Vol. 1.7, Page 2

Each vial contains 20 mg doxorubicin HCl at a concentration of 2.0 mg/mL and a pH of 6.5. Vol. 1.4, Page 2, Table D.iii.1

The Stealth liposome carriers are composed of N-(Carbamoyl-methoxypolyethylene glycol 2000)-1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), fully hydrogenated soy phosphatidylcholine (HSPC), and cholesterol. Vol. 1.4, Page 1, Table D.ii.1

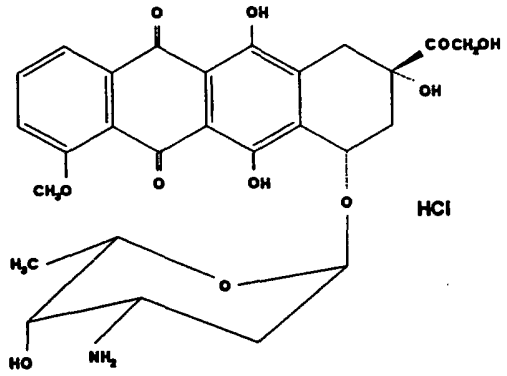
Other ingredients are sucrose, ammonium sulfate, and histidine. Vol. 1.4, Page 2, Table D.iii.1

Greater than 90% of the drug is encapsulated in the Stealth liposomes. Vol. 1.7, Page 2

DOX-SL is preservative-free. Vol. 1.4, Page 2, Table D.iii.1

Doxorubicin hydrochloride is designated chemically as (8S,10S)-10-[(3-Amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-8-glycoloyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride. Vol. 1.2, Page 24

Doxorubicin HCl has the following structural formula: Vol. 1.2, Page 24



The molecular formula of the drug is $C_{27}H_{29}NO_{11}\cdot HCl$; its weight is 579.99. Vol. 1.2, Page 24

CLINICAL PHARMACOLOGY

Mechanism of Action

The active ingredient of DOX-SL is doxorubicin HCl.

The mechanism of action of doxorubicin is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis.

ADRIAMYCIN PFS™ Package Labeling. In: *Physician's Desk Reference®*. 47th ed. Montvale, NJ: Medical Economics Data; 1993: 560 - 561.

Cell culture studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations.

DOX-SL is doxorubicin HCl encapsulated in long-circulating Stealth liposomes.

Vol. 1.17, Page 1

Stealth liposomes are microscopic vesicles composed of a lipid bilayer that contains surface-bound methoxy polyethylene glycol (MPEG).

Vol. 1.4, Page 1, Table D.ii.1

The hydrophilic MPEG molecules on the liposome surface inhibit binding of plasma proteins to the Stealth liposomes, decrease the interaction of the liposomes with endothelial cells, and reduce the uptake of the liposomes by the macrophages of the mononuclear phagocytic system (MPS).

Vol. 1.317, Page 20
Vol. 1.317, Page 40
Vol. 1.320, Page 57
Vol 1.313, Page 43

This results in a significantly increased blood circulation time compared to conventional liposomes and doxorubicin HCl, USP. Stealth liposomes have a half-life up to approximately 55 hours in humans.

Vol. 1.51, Page 64
Vol. 1.52, Page 1
Vol. 1.320, Page 80
Vol. 1.57, Page 49, Table 11

They are stable in blood, and direct measurement of liposomal doxorubicin shows that greater than 90%-95% of the drug remains liposome-encapsulated during circulation. However, the assay used cannot quantify less than 5%-10% free doxorubicin, and pharmacokinetic modeling suggests that more than 99% of the doxorubicin remains within the liposome. (See Pharmacokinetics.)

Vol. 1.51, Page 166, Table 1
Vol. 1.321, Page 202
Vol. 1.51, Page 172
Vol. 1.56, Page 64

It is hypothesized that by virtue of their increased circulation time and reduced clearance, the small DOX-SL liposomes have an increased likelihood of extravasation through the altered and often compromised vasculature of many types of tumors.

Vol. 1.317, Page 20
Vol. 1.320, Page 137
Vol. 1.320, Page 143
Vol. 1.316, Page 1
Vol. 1.319, Page 1
Vol. 1.315, Page 114

This hypothesis is supported by studies using colloidal gold-containing Stealth liposomes, which can be visualized microscopically.[1]

Vol. 1.331, Page 8

Evidence of extravasation of Stealth liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C26 colon carcinoma tumors and in transgenic mice with Kaposi's sarcoma-like lesions. Vol. 1.315, Page 237 Vol. 1.315, Page 220

In mice, release of doxorubicin from the Stealth liposomes accumulated in the tumor accounts for the improved anti-tumor efficacy of DOX-SL compared to doxorubicin HCl, USP. Vol. 1.52, Page 206

Pharmacokinetics Vol. 1.57, Page 1

The plasma pharmacokinetics of DOX-SL were evaluated in 42 patients with Kaposi's sarcoma who received single doses of 10 or 20 mg/m^2 administered by a 30-minute infusion.

The following values were observed after the 10 and 20 mg/m^2 doses of DOX-SL.

Vol. 1.57, Page 49, Table 11

Pharmacokinetic Parameters in DOX-SL-Treated Patients

Parameter	Mean ± Standard Error	
	DOX-SL 10 mg/m^2 (n=23)	DOX-SL 20 mg/m^2 (n=23)
Maximum Plasma Concentration[a] (μg/mL)	4.12 ± 0.215	8.34 ± 0.490
Plasma Clearance (L/h/m^2)	0.0572 ± 0.0103	0.0419 ± 0.00401
Volume of Distribution (L/m^2)	2.84 ± 0.124	2.77 ± 0.129
AUC (μg/mL·h)	252 ± 28.5	577 ± 57.2
λ_1 half-lives (hours)	5.80 ± 1.07	5.61 ± 1.21
λ_2 half-lives (hours)	50.1 ± 5.71	56.6 ± 5.74

[a] Measured at end of 30-minute infusion.

The plasma pharmacokinetics of DOX-SL in humans differed significantly from those reported in the literature for doxorubicin HCl, USP. Doxorubicin HCl, USP displays extensive tissue distribution (volume of distribution, 700-1100 L/m^2), rapid plasma clearance (24-35 L/h/m^2), and a terminal half-life of 28 hours.[2,3] In contrast to the pharmacokinetics of doxorubicin HCl, the pharmacokinetic profile of DOX-SL indicates that

Vol. 1.331, Page 48

Vol. 1.331, Page 12

DOX-SL is confined mostly to the vascular fluid volume and that the elimination of doxorubicin is dependent upon the liposomal carrier. However, doxorubicin becomes available after the liposomes are extravasated and enter the tissue compartment. Consequently, at equivalent doses, the plasma concentration and AUC values of DOX-SL are significantly higher than those achieved with doxorubicin HCl, USP.

Kaposi's sarcoma lesion and normal skin biopsies were obtained 48 and 96 hours post-infusion. Drug levels in the lesions were 3- to 14-fold higher compared to the normal skin. In another study, patients received equal doses of doxorubicin HCl or DOX-SL. The concentration of doxorubicin HCl in the KS lesions biopsied 72 hours after dosing was 5-11 times higher in patients receiving DOX-SL compared to levels in patients receiving doxorubicin HCl.

Vol. 1.57, Page 1

Vol. 1.57, Page 52, Table 14

Vol. 1.60, Page 1

Vol. 1.60, page 40, Table 9

Clinical Studies

Vol. 1.64, Page 1

In two open-label studies, the majority of patients with AIDS-related Kaposi's sarcoma were treated with 20 mg/m^2 every three weeks.

Vol. 1.74, Page 1

The first study included 136 patients. Of these patients, 41 were considered "failed or intolerant." Patients were defined as failed or intolerant to prior treatment either because their disease progressed after receiving at least 2 cycles of combination systemic chemotherapy (e.g., bleomycin and vincristine or Adriamycin, bleomycin and vincristine) or because they were intolerant to continued combination chemotherapy as evidenced by unacceptable toxicity. Vol. 1.64, Page 35

These 41 patients are noted as failed or intolerant patients in the following table. Twenty-six of these 41 patients had received prior doxorubicin HCl (Adriamycin). Vol. 1.64, Page 35

Of these 41 failed or intolerant patients treated with DOX-SL, 27 patients, based on the primary analysis of 5 indicator lesions, had a partial response, 10 had stable disease, and 4 had disease progression as their best response. Among the 26 patients who received prior doxorubicin in combination with bleomycin and a vinca alkaloid, 16 had a partial response, 7 had stable disease, and 3 had disease progression as their best response. Vol. 1.64, Page 38 Vol. 1.64, Page 91, Table 11 Vol. 1.64, Page 94, Table 14

The median number of cycles needed to reach a partial response was 4. The median duration of partial response, measured from the day of response, was 78 days.

Vol. 1.64, Page 93, Table 13

In addition, these failed or intolerant patients had significant improvement over baseline in KS lesion pain, color, edema, and flattening of lesions.

Vol. 1.64, Page 40

A second study conducted in Europe and Australia included 238 AIDS-KS patients at doses of 10 to 20 mg/m^2 every two weeks. In this study the proportion of responders (partial and complete) was 80.7%.

Vol. 1.74, Page 1

Vol. 1.74, Page 104, Table 13

Response and duration of response for these studies are summarized in the tables below.

Vol. 1.64, Page 91, Table 11

Vol. 1.64, Page 126, Table 43

Vol. 1.74, Page 104, Table 13

Clinical Response in Patients with AIDS-KS

	Study 30-12 Failed or Intolerant Patients	Study 30-12 All Patients	Study 30-03 All Patients
Number of Patients	41	136	238
Best Response			
Complete	0	0	15 (6.3%)
Partial	27 (65.9%)	84 (61.8%)	177 (74.4%)
Stable	10 (24.4%)	36 (26.5%)	44 (18.5%)
Progression	4 (9.8%)	16 (11.8%)	2 (0.8%)

Duration of Response in Patients with AIDS-KS

Vol. 1.64, Page 93, Table 13

Vol. 1.64, Page 128, Table 45

Vol. 1.74, Page 106, Table 15

	Study 30-12 Failed or Intolerant Patients	Study 30-12 All Patients	Study 30-03 All Patients
Number of Patients	41	136	238
Duration of PR and/or CR (Days)			
Mean (SE)	86.6 (10.69)	82.0 (6.85)	117.2 (7.13)
Median	78.0	75.0	91.0

Note: Mean, SE, and median are Kaplan-Meier estimates.

INDICATIONS AND USAGE

Vol. 1.64, Page 1

Vol. 1.74, Page 1

DOX-SL is indicated for AIDS-related Kaposi's sarcoma in patients who have failed prior systemic combination chemotherapy either due to progression of disease or unacceptable toxicity.

CONTRAINDICATIONS

DOX-SL is contraindicated in patients who have a history of hypersensitivity reactions to doxorubicin HCl, USP or the components of DOX-SL.

WARNINGS

Vol. 1.92, Page 94

Experience with DOX-SL is limited in evaluating cardiac risk. Therefore warnings related to use of doxorubicin HCl, USP should be observed.

Vol. 1.92, Page 125, Table 14

With doxorubicin HCl, USP serious irreversible myocardial toxicity with delayed congestive failure often unresponsive to any cardiac supportive therapy may be encountered as total dosage of doxorubicin in any formulation approaches 550 mg/m^2. Caution should be observed in patients who have received other anthracyclines.

ADRIAMYCIN PFS™ Package Labeling. In: *Physician's Desk Reference®*. 47th ed. Montvale, NJ: Medical Economics Data; 1993: 560 - 561.

This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy.

Until more information is known, cardiac function should be carefully monitored in patients treated with DOX-SL.

Patients with a history of cardiovascular disease should be administered DOX-SL only when the benefit outweighs the risk to the patient.

Radiation-induced toxicity to the myocardium, mucosae, skin and liver have been reported to be increased by the administration of doxorubicin HCl, USP.

ADRIAMYCIN PFS™ Package Labeling. In: *Physician's Desk Reference®*. 47th ed. Montvale, NJ: Medical Economics Data; 1993: 560 - 561.

Infusion-associated reactions characterized by flushing, shortness of breath, facial swelling, back pain and/or hypotension have occurred in approximately 6.4% (29/452) of patients treated with DOX-SL.

Vol. 1.92, Page 90

These reactions resolved over the course of several hours once the infusion was terminated.

DOX-SL contains doxorubicin HCl which is known to lower peripheral blood counts. Severe myelosuppression may occur.

ADRIAMYCIN PFS™ Package Labeling. In: *Physician's Desk Reference®*. 47th ed. Montvale, NJ: Medical Economics Data; 1993: 560 - 561.

At some time during treatment, 38% of patients required G-CSF (or GM-CSF) to support their blood counts.

Vol. 1.92, Page 123, Table 13

Appropriate monitoring of blood counts should be conducted while treating patients with DOX-SL.

Dosing may need to be modified based on patients' blood counts.

Although not formally studied, DOX-SL, like doxorubicin HCl, USP; may potentiate the toxicity of other anti-cancer therapies. Exacerbation of cyclophosphamide-induced hemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with doxorubicin HCl, USP.

DOX-SL dosage should be reduced in patients with impaired hepatic function.

Prior to DOX-SL administration, evaluation of hepatic function is recommended using conventional clinical laboratory tests such as SGOT, SGPT, alkaline phosphatase and bilirubin (See DOSAGE AND ADMINISTRATION, Patients with Impaired Hepatic Function).

ADRIAMYCIN PFS™ Package Labeling. In: *Physician's Desk Reference®*. 47th ed. Montvale, NJ: Medical Economics Data; 1993: 560 - 561.

PRECAUTIONS

Injection Site Effects

Although DOX-SL should be considered a vesicant, animal experience indicates that extravasation injury of DOX-SL is less severe than with doxorubicin HCl, USP.

Vol. 1.46, Page 1

If any signs or symptoms of extravasation occur, the infusion should be immediately terminated and restarted in another vein.