No local necrosis following extravasation has been seen with DOX-SL in humans.

Other Effects Vol. 1.92, Page 89

In several studies (N=452) 1.5% of patients developed palmar - plantar skin eruptions characterized by often painful, macular reddening. This event appears to be dose-related and clears in one to two weeks with or without treatment with corticosteroids.

Laboratory Tests

Frequent complete blood counts are recommended.

Drug Interactions

No formal drug interaction studies have been conducted with DOX-SL. However, caution should be exercised in the concomitant use of drugs known to interact with doxorubicin HCl. Vol. 1.92, Page 97

Caution should be exercised when giving any other cytotoxic agents, especially myelotoxic agents, at the same time.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Although no studies have been conducted with DOX-SL, doxorubicin HCl, USP and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models.[4,5]

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Stealth liposomes (not containing drug) are neither mutagenetic nor genotoxic.

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The possible adverse effects on fertility in males and females in humans or experimental animals have not been adequately evaluated.

Pregnancy

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Pregnancy Category C. DOX-SL is embryotoxic in rats and embryotoxic and abortifacient in rabbits.

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There is no experience in pregnant women with DOX-SL.

DOX-SL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk.

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from DOX-SL, mothers should discontinue nursing prior to taking this drug.

Pediatric Use

The safety and effectiveness in patients less than 18 years of age have not been established.

ADVERSE REACTIONS Vol. 1.92, Page 40, Table 8

The following adverse events are based on the experience of 435 patients with AIDS-related KS, the majority of whom were treated with 20 mg/m^2 every 2 to 3 weeks for a total of 3,011 doses. These patients were enrolled in four trials of patients with AIDS-felated Kaposi's sarcoma.

Of the 435 patients in these clinical trials, 79% experienced adverse events possibly or probably related to the use of DOX-SL. Vol. 1.92, Page 168, Table 20

Adverse events related to the use of DOX-SL that were reported in 5% or more of patients are summarized in the table below:

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

Vol. 1.92, Page 168, Table 20

	Total
Number of Patients	435
Number of Patients Reporting Adverse Events	345 (79.3%)
Number of Patients by COSTART Preferred Term Incidence	
Leukopenia	254 (58.4%)
Anemia	75 (17.2%)
Nausea	65 (14.9%)
Alopecia	45 (10.3%)
Fever	41 (9.4%)
Hypochromic Anemia	41 (9.4%)
Diarrhea	36 (8.3%)
Alkaline Phosphatase Increased	32 (7.4%)
Asthenia	30 (6.9%)
Oral Moniliasis	30 (6.9%)
Thrombocytopenia	30 (6.9%)
Stomatitis	28 (6.4%)
Vomiting	27 (6.2%)
Headache	26 (6.0%)
SGPT Increased	23 (5.3%)

The following adverse events considered by the investigator to be possibly or probably related to DOX-SL, occurred in 1% to 5% of patients:

Body As A Whole: Abdominal pain, allergic reaction, chest pain, face edema, infection, pain.

Cardiovascular System: Hypotension, vasodilatation.

Digestive System: Constipation, dysphagia, glossitis,

abnormal liver function tests, mouth ulceration, nausea and vomiting.

Hemic And Lymphatic System: Eosinophilia, hemolysis, prothrombin increased.

Metabolic/Nutritional Disorders: Bilirubinemia, hypocalcemia, SGOT increased, weight loss.

Nervous System: Dizziness, emotional lability, somnolence.

Respiratory System: Dyspnea, pneumonia.

Skin And Appendages: Herpes simplex, rash, skin ulcer.

Special Senses: Retinitis.

Urogenital System: Albuminuria.

The following adverse events considered by the investigator to be possibly or probably related to DOX-SL, occurred in <1% of patients:

Body As A Whole: Abscess, ascites, back pain, cellulitis, substernal chest pain, chills, flu syndrome, hypothermia, immune system disorder, injection site reaction, malaise, moniliasis, mucous membrane disorder, neoplasm, sepsis.

Cardiovascular System: Bundle branch block, cardiomyopathy, cardiovascular disorder, deep thrombophlebitis, heart failure, hemorrhage, migraine, palpitation, pericardial effusion, peripheral vascular disorder, phlebitis, syncope, tachycardia, thrombophlebitis,

thrombosis, ventricular arrhythmia, ventricular extrasystoles.

Digestive System: Anorexia, aphthous stomatitis, cholestatic jaundice, colitis, dyspepsia, esophageal ulcer, esophagitis, gastritis, gastrointestinal hemorrhage, gingivitis, hematemesis, hepatic failure, hepatitis, hepatosplenomegaly, increased appetite, leukoplakia of the mouth, liver damage, pancreatitis, rectal disorder, sclerosing cholangitis, ulcerative proctitis, ulcerative stomatitis.

Endocrine System: Diabetes mellitus.

Hemic And Lymphatic System: Abnormal erythrocytes, lymphadenopathy, lymphangitis, lymphedema, marrow depression, pancytopenia, thromboplastin decreased.

Metabolic/Nutritional Disorders: Creatinine increased, dehydration, edema, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, lactic dehydrogenase increased, peripheral edema, weight gain.

Musculoskeletal System: Arthralgia, bone disorder, bone pain, myalgia, myositis.

Nervous System: Acute brain syndrome, anxiety, confusion, convulsion, depression, hemiplegia, hypokinesia, hypotonia, insomnia, meningitis, nervousness, neuropathy, paresthesia, peripheral neuritis, reflexes decreased, speech disorder, abnormal thinking, vertigo.

Respiratory System: Bronchitis, cough increased, hyperventilation, lung disorder, pharyngitis, pleural disorder, pleural effusion, pneumothorax, rhinitis, sinusitis.
Skin And Appendages: Application site reaction, cutaneous moniliasis, eczema, erythema multiforme, erythema nodosum, exfoliative dermatitis, fungal dermatitis, furunculosis, herpes zoster, maculopapular rash, pruritus, pustular rash, skin discoloration, sweating, vesiculobullous rash.
Special Senses: Blindness, conjunctivitis, eye pain, optic neuritis, otitis media, tinnitus.
Urogenital System: Balantitis, cystitis, dysuria, genital edema, glycosuria, hematuria, kidney failure, prostatic disorder, testis disorder.

There were 13 patient withdrawals due to an adverse event. Six of these patients withdrew due to acute infusion-related reactions. Four patients withdrew due to neutropenia; two due to cardiovascular adverse events unrelated to DOX-SL; and one due to an unidentified unacceptable toxicity.

OVERDOSAGE

Acute overdosage with doxorubicin HCl, USP enhances the toxic effects of 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.

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

DOSAGE AND ADMINISTRATION

Vol. 1.64, Page 1

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DOX-SL should be administered intravenously as 20 mg/m^2 over 30 minutes every two to three weeks.

Do not administer as a bolus injection or an undiluted solution.

Each vial contains 20 mg doxorubicin HCl at a concentration of 2.0 mg/mL.

Vol. 1.4, Page 2, Table D.iii.1

Preparation for Intravenous Administration

The appropriate dose of DOX-SL must be diluted in 250 mL of 5% Dextrose Injection, USP prior to administration.

The use of any diluent other than 5% Dextrose Injection, or the presence of any bacteriostatic agent such as benzyl alcohol may cause precipitation.

Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in DOX-SL.

Do not mix with other drugs.

Do not use if a precipitate or foreign matter is present.

Patients with Impaired Hepatic Function

Limited clinical experience exists in treating hepatically impaired patients with DOX-SL.

Therefore, based on experience with doxorubicin HCl, it is recommended that DOX-SL dosage be reduced if the bilirubin is elevated as follows: Serum bilirubin 1.2-3.0 mg/dL give 1/2 normal dose, >3 mg/dL give 1/4 normal dose.

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

Storage and Stability Vol. 1.10, Page 8

Store unopened vials of DOX-SL at 2°C to 8°C (36°F to 46°F).

Prior to use, store diluted DOX-SL for infusion at 2°C to 8°C (36°F to 46°F) for no longer than 8 hours. Vol. 1.10, Page 8

Procedure for proper handling and disposal

Caution should be exercised in handling DOX-SL solution.

The use of gloves is required.

If DOX-SL comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

DOX-SL should be handled and disposed of in a manner consistent with that of other anti-cancer drugs.

Several guidelines on this subject exist[6-8] although there is no general agreement that all of the procedures listed in these guidelines are appropriate or necessary. Vol. 1.331, Page 32 Vol. 1.331, Page 36 Vol. 1.331, Page 1

HOW SUPPLIED

Vol. 1.7, Page 2

DOX-SL (pegylated liposomal doxorubicin HCl) Injection is supplied as a sterile, translucent, red suspension in 10 mL glass, single use vials.

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

Vol. 1.4, Page 2, Table D.iii.1

Available as individually cartoned vials in packages of 10. NDC #0000-0000-00.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Vol. 1.18, Page 53

Animal studies have shown that DOX-SL has greater anti-tumor efficacy than doxorubicin HCl, USP in a variety of tumor models, including murine models of colon and mammary carcinoma and human xenograft models of ovarian, prostatic and non-small cell lung cancer. In every model evaluated, DOX-SL was more effective than equal doses of doxorubicin HCl, USP at inhibiting or halting tumor growth, effecting cures, and/or prolonging survival times of tumor-bearing animals.

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Most often, all three endpoints were improved by DOX-SL, and in no case was DOX-SL less effective than doxorubicin HCl, USP. In general, the efficacy of doxorubicin HCl, USP was limited by its toxicity, and DOX-SL could be used at a higher dose.

In animal toxicology studies, qualitatively similar adverse effects were seen after administration of DOX-SL and doxorubicin HCl, USP, but generally occurred at a lower frequency and severity in DOX-SL-treated animals. Vol. 1.20, Page 1 Vol. 1.21, Page 1

DOX-SL produced fewer histopathologic cardiac lesions in rats and dogs than an equal cumulative dose of doxorubicin HCl, USP. Vol. 1.28, Page 23 Vol. 1.35, Page 1

Myelotoxicity was marginally less severe in DOX-SL-treated animals than with doxorubicin HCl, USP.

Repeated dosing of rats and dogs with DOX-SL induced cutaneous ulcerative lesions, principally on the feet and legs of both rats and dogs.

The lesions resolved within 10-14 days after cessation of treatment, and both their incidence and severity could be reduced by decreasing the dose or lengthening the dose interval.

These lesions are similar to skin lesions (hand-and-foot syndrome) described in human patients who receive continuous or long-term infusions of doxorubicin HCl, USP.[9]

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Tolerance to extravasation of DOX-SL was evaluated in animal models versus doxorubicin HCl, USP.

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Lesions that were induced were minor and reversible compared to more severe and irreversible lesions after extravasation of doxorubicin HCl, USP. (See PRECAUTIONS, Injection Site Effects)

REFERENCES

1. Hong K., Friend DS, Glabe CG, Papahadjopoulos D. Liposomes containing colloidal gold are a use probe of liposome - cell interactions. *Biochim Biophys Acta.* 1983; 372:320-323. Vol. 1.331, Page 8

2. Speth PAJ, van Hoesel QGCM, Haanen C. Clinical pharmacokinetics of doxorubicin. *Clin Pharmacokinetics.* 1988; 15:15-31. Vol. 1.331, Page 48

3. Jacquet JM, et al. Doxorubicin and doxorubicinol: intra- and inter-individual variations of pharmacokinetic parameters. *Cancer Chemother Pharmacol* 1990; 27:219-225. Vol. 1.331, Page 12

4. Maral RJ and Jouanne M. Toxicology of daunorubicin in animals and man. *Cancer Treat Rep.* 1981; 65 (Suppl. 4):9-18. Vol. 1.331, Page 22

5. Wright JC. Cancer chemotherapy: Past, present and future - Part I. *J Nat Med Assoc.* 1984; 76:773-784 Vol. 1.331, Page 65

6. Recommendations for the Safe Handling of Cytotoxic Drugs. NIH Publication No.92-2621. US Government Printing Office, Washington, DC 20402. Vol. 1.331, Page 32

7. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm.* 1986; 43:1193-1204. Vol. 1.331, Page 36

8. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm.*1985; 42:131-137. Vol. 1.331, Page 1

9. Lokich JJ, Moore C. Chemotherapy-associated palmar-plantar erythrodysesthesia syndrome. *Annals Int Med.* 1984; 101:798-800.

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II. PHARMACOLOGIC CLASS, SCIENTIFIC RATIONALE AND INTENDED USE

A. Pharmacologic Class of Drug Substance

DOXIL (Stealth® Liposomal Doxorubicin Hydrochloride) is a long-circulating ("Stealth") liposome formulation. The active drug substance encapsulated in DOXIL liposomes is doxorubicin hydrochloride, (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, a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*. Doxorubicin interacts strongly with nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix, and inhibits DNA and RNA metabolism in vitro and in vivo.[1,2] Although doxorubicin HCl has limited antibacterial activity (with minimal inhibitory concentrations in the 1-100 μg/mL range), concentrations at which the drug exerts its cytotoxic action on rapidly proliferating tumor cells is lower (generally <1 μg/mL). Cell culture studies have demonstrated rapid cell penetration, perinucleolar chromatin binding and rapid inhibition of mitotic activity and nucleic acid biosynthesis.

B. Scientific Rationale

Doxorubicin HCl (which is often referred to by its trade name Adriamycin®) is an approved antineoplastic agent and has been in clinical use for over 20 years. Human tumors shown to be responsive to doxorubicin HCl include acute leukemia, resistant Hodgkin's and non-Hodgkin's lymphomas, sarcoma, neuroblastoma, ovarian and endometrial carcinoma, breast carcinoma, bronchogenic carcinoma, lung cancer and thyroid and bladder carcinoma.[3] AIDS-related Kaposi's sarcoma (KS) is somewhat responsive to Adriamycin as a single agent and in combination regimens.[4,5] Dose dependent toxicities, including stomatitis/mucositis, nausea/vomiting, bone marrow suppression and cardiomyopathy, limit the amount of Adriamycin patients are able to tolerate.

Tumors, including the cutaneous and visceral lesions characteristic of KS, depend on blood vessels for exchange of gases, nutrients, and metabolic waste products. Neovascularization is necessary to support tumors larger than a few millimeters in diameter. The permeability of vessels in tumors is significantly higher than those residing in normal tissues.[6] Vessels supplying KS lesions are particularly permeable as evidenced by edema and extensive extravasation of formed blood elements (perivascular streams of extravasated red blood cells are typically seen in KS lesions).[7] This increased vascular permeability has been attributed to several factors: the existence of fenestrated and

discontinuous capillaries, the existence of blood channels without an endothelial lining,[8] increased occurrence of trans-endothelial channels and higher trans-endothelial pinocytotic transport.[9]

Conventional liposomal formulations of doxorubicin have been proposed as a means to reduce doxorubicin HCl-related toxicities and thereby improve the drug's therapeutic index. The scientific rationale for the use of liposomal formulations of doxorubicin HCl is discussed below, first for conventional liposomes and then for Stealth liposomes.

1. Conventional Liposomes

Conventional liposomes used for drug delivery purposes are generally small in size (< 300 nm) and composed of naturally occurring or synthetic phospholipids, with or without cholesterol. The exposed outer surfaces of such liposomes are susceptible to attack and destabilization by components present in biological fluids. Following intravenous injection, a liposome of this type is rapidly recognized as a foreign body and cleared from circulation in a dose-dependent fashion by elements of the immune system: primarily by specialized phagocytic cells residing in the liver and spleen, the mononuclear phagocyte system (MPS). It is believed that binding of plasma proteins (lipoproteins, immunoglobulins, complement) to the liposome surface triggers such macrophage uptake.

Internalization of liposome-encapsulated antitumor agents by MPS cells has the potential to diminish exposure of other body tissues to the irritating effects of such drugs. Liposomal encapsulation of doxorubicin has been proposed as a means of reducing the side effects of this highly active antitumor agent. By taking advantage of MPS clearance of encapsulated drug, exposure of other healthy tissues to high plasma concentrations of doxorubicin is reduced. Doxorubicin-related nausea/vomiting and cardiomyopathy are related to the drug's peak levels in plasma. By using liposome encapsulation to sequester the majority of an injected dose in the MPS, in theory, plasma levels of free drug are attenuated and safety improved. The drug is eventually released from MPS organs and distributes to peripheral tissues in free form. In this case, the pharmacokinetic pattern is intended to mimic that seen following administration of doxorubicin as a divided-dose or prolonged infusion, regimens known to reduce drug-related side effects.[10-15] Indeed, it has been shown that administration of liposome-encapsulated doxorubicin reduces the drug's acute and chronic toxicities in preclinical animal models.[16] Moreover, results from animal models indicate that doxorubicin delivered in this fashion retains its activity against non-hepatic tumors.[17] The pharmacokinetics and safety of various clinical formulations of conventional liposomal doxorubicin have been reported in the scientific literature.[16,18-36] Clinical pharmacokinetic measurements confirm that conventional liposome formulations

are cleared rapidly from plasma. These data also suggest that a considerable amount of encapsulated doxorubicin HCl is released into plasma *prior* to MPS uptake.[22,33]

2. Long-circulating "Stealth" Liposomes

Recognizing that rapid liposome clearance, coupled with release of encapsulated drug, severely limits the potential of liposomes to transport *encapsulated* drug to systemic tumors, strategies have been sought to stabilize liposomes in plasma and prolong their circulation following administration. Similarly, efforts have been made to optimize liposome size.[37-40]

DOXIL is a long-circulating "Stealth" liposomal formulation of doxorubicin HCl. This new type of liposome contains surface-grafted segments of the hydrophilic polymer methoxypolyethylene glycol (MPEG). These linear MPEG groups extend from the liposome surface creating a protective coating that reduces interactions between the lipid bilayer membrane and plasma components. A schematic representative of a Stealth liposome, not drawn to scale, is presented in Figure 1.

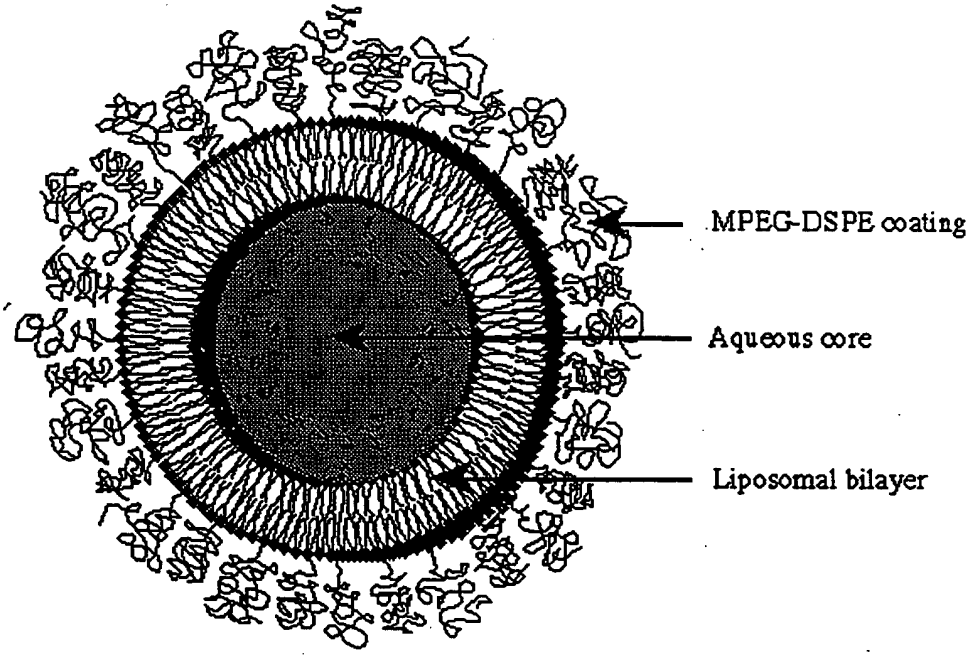

Figure 1 Diagram of PEG-stabilized "Stealth" Liposome

The critical design features of the Stealth liposome include:

- Polyethylene glycol ("Stealth" polymer) coating: reduces MPS uptake and provides long plasma residence times.
- Average diameter of approximately 100 nm: balances drug carrying capacity and circulation time, and allows extravasation through endothelial defects/gaps in tumors.
- Low permeability lipid matrix and internal aqueous buffer system: provide high drug loading and stable encapsulation, i.e., drug retention during residence in plasma.

The "steric stabilization" effect provided by MPEG is believed to be responsible for the remarkable stability of DOXIL in plasma. The MPEG coating also inhibits the interaction (close approach) of liposomes with macrophage cells, thus reducing hepatic uptake and prolonging liposome residence time in the circulation.[41] Comparative pharmacokinetic measurements in rodents and dogs indicate that doxorubicin HCl has a prolonged plasma residence time when administered as DOXIL relative to Adriamycin (15 to 30 hours, compared to a distribution half-life of 10 minutes for Adriamycin).[42] The long residence time of DOXIL was confirmed in studies conducted in cancer patients and AIDS patients with KS.[43-44] These studies are described further in this Overall NDA Summary in Section VI: Human Pharamcokinetic Summary. In these studies, DOXIL remained in circulation with a distribution half-life of 40 to 50 hours while the distribution half-life of doxorubicin HCl is reported to be less than 10 minutes.

Light and electron microscopic examination of C-26 colon carcinoma and KS-like lesions show high concentrations of liposomes in interstitial areas surrounding capillaries in mice treated with Stealth liposomes containing colloidal gold particles as a liposome marker. These findings suggest that such Stealth liposomes circulate for a sufficient period of time and are small enough to extravasate through the capillaries supplying tumors.[45,46]

Following treatment of tumor-bearing mice with DOXIL, doxorubicin concentrations achieved in tumors are higher and anti-tumor activity is greater compared to animals receiving comparable doses of unencapsulated drug.[47-51] These findings suggest that DOXIL, by virtue of its plasma stability and slow clearance, might have a higher therapeutic ratio than earlier liposome formulations of doxorubicin. Relative to free doxorubicin, DOXIL treatment resulted in a 4- to 16-fold enhancement of drug levels in malignant effusion (fluid accumulated in tissues or body cavities as result of malignant growth) obtained from cancer patients.[43] Similar tumor localization results were also

obtained in AIDS patients with KS.[44] Clinical experience suggests DOXIL is active against advanced AIDS-related KS.[52-55]

In addition to increasing doxorubicin localization in tumor tissues, the encapsulation of doxorubicin in Stealth liposomes could also result in the reduction of some of the adverse reactions associated with doxorubicin HCl administration. For example, the cardiotoxicity caused by high cumulative doses of doxorubicin is believed to be related to the high peak plasma concentration of doxorubicin HCl after its administration using the standard 3-week schedule. It is well established in the literature that the incidence of cardiomyopathy is significantly reduced when the drug is administered using a 1-week or a prolonged infusion schedule.[10-15] The encapsulation of doxorubicin HCl will effectively reduce the peak drug concentration in plasma, therefore mimicking the prolonged infusion regimen. Indeed, a significant reduction in cardiotoxicity was observed in rats and dogs after a multiple dose treatment with DOXIL when compared to an equal dose of doxorubicin HCl.[56,57]

C. Intended Use of DOXIL

The proposed indication for DOXIL sought in this NDA is treatment of AIDS patients with advanced Kaposi's sarcoma who have failed standard first-line systemic chemotherapy due to disease progession or unacceptable toxicity. These patients have no clearly proven treatment options. It is believed that the higher lesion concentrations of doxorubicin achieved with DOXIL will provide such patients with effective therapy and lessen the risk of toxicities associated with multi-agent regimens.

D. Summary

Although doxorubicin HCl is active against KS, it is usually not administered as a single agent: combinations with bleomycin and/or a vinca alkaloid such as vincristine are preferred clinically because these provide higher response rates. Administration of multiple courses of these combinations often leads to therapeutic failures due to patients' intolerance to the drugs (leukopenia, alopecia, neuropathy, pulmonary complications and/or the interaction of these drugs with other AIDS-related conditions such as neuropathy). In some patients, KS progresses despite aggressive combination chemotherapy. Such patients have no clearly proven treatment options.

DOXIL is a "Stealth" liposome formulation of doxorubicin HCl. Surface grafted MPEG-polymer allows DOXIL liposomes to circulate for prolonged periods in the blood stream. The DOXIL lipid matrix and internal buffer system combine to keep doxorubicin encapsulated during liposome residence in the circulation. DOXIL liposomes are small

enough to pass intact through defective blood vessels supplying KS lesions. Relative to conventional doxorubicin HCl, this extravasation uptake mechanism leads to higher lesion concentrations of drug after DOXIL administration.

The encapsulated drug is released after extravasation in KS lesions and enters surrounding tumor cells, exerting its cytotoxic action. The greater tumor concentration provided by DOXIL provides favorable response/clinical benefit, even for patients who fail first-line doxorubicin HCl-containing regimens.

III. MARKETING HISTORY

DOXIL® (Stealth® liposomal doxorubicin HCl) Injection has not been approved for commercial distribution in any foreign country nor are any applications currently under review. In accordance with local regulations, DOXIL is available on a Named Patient Sale basis in Austria, Ireland, the United Kingdom, Israel and Italy. The pertinent local legislation is listed in Table 1.

TABLE 1
Countries where DOXIL Injection
is Available Under Named Patient Sale

Country	Regulating Body	Legislation
Austria	Ministry of Health	Medicines Law, AMG 83 § 12
Ireland	National Drug Advisory Board (NDAB)	None[a]
Israel	Ministry of Health, Pharmaceutical Division	Regulation 29(G)
Italy	Ministry of Health	None[b]
United Kingdom	Medicines Control Agency (MCA)	Statutory Instrument 1984 No. 673; MEDICINES; The Medicines (Exemption from Licenses)(Importation) Order 1984

[a] The National Drug Advisory Board (NDAB) requires a physician to submit either an oral or written request for treatment of a Named Patient with an unlicensed medicine. At the discretion of the NDAB, a letter of "no objection" may be provided.

[b] There are no specific governmental regulations concerning the prescribing of unlicensed medicines in Italy. A prescription and letter stating that no alternative medicines are available in Italy is received from the physician prior to shipment of the drug product.

As of July 1994, there have been a total of 28 patients treated under the Named Patient Sale program. Details by country are provided in Table 2.

TABLE 2
Number of Patients Treated by Country
Under Named Patient Use Program

Country	Number of Patients
Austria	8
Ireland	10
Israel	2
Italy	1
United Kingdom	7
TOTAL	28