

# ドキシル注20mgに関する資料

本資料に記載された情報に係る権利及び内容の責任はヤンセンファーマ株式会社に帰属するものであり、当該情報を適正使用以外の営利目的に利用することはできません。

ヤンセン ファーマ株式会社

CL55-LTI-30-SM-94-55

**CONFIDENTIAL**

**OVERALL NDA SUMMARY:**

**DOXIL® (STEALTH® LIPOSOMAL DOXORUBICIN HYDROCHLORIDE)**

**August 29, 1994**

**Liposome Technology, Inc.  
960 Hamilton Court  
Menlo Park, California 94025**

TABLE OF CONTENTS

	<u>Page</u>
<b>I. ANNOTATED PACKAGE INSERT .....</b>	<b>1</b>
<b>II. PHARMACOLOGIC CLASS, SCIENTIFIC RATIONALE AND INTENDED USE.....</b>	<b>31</b>
A. Pharmacologic Class of Drug Substance .....	31
B. Scientific Rationale.....	31
1. Conventional Liposomes .....	32
2. Long-circulating "Stealth" Liposomes .....	33
C. Intended Use of DOXIL.....	35
D. Summary .....	35
<b>III. MARKETING HISTORY .....</b>	<b>37</b>
<b>IV. SUMMARY OF THE CHEMISTRY, MANUFACTURING AND CONTROLS DATA.....</b>	<b>39</b>
A. Drug Substance .....	39
B. Drug Product.....	40
1. Specifications and Analytical Methods for Drug Product Ingredients .....	41
2. Manufacturer Information.....	42
3. Method of Manufacture and Packaging .....	42
4. Regulatory Specifications and Testing Procedures for Acceptance of the Drug Product.....	43
5. Container-Closure System .....	44
6. Microbiology.....	44
7. Drug Product Stability .....	44
8. Environmental Assessment.....	44
C. Investigational Formulae .....	45
<b>V. SUMMARY OF THE NONCLINICAL PHARMACOLOGY AND TOXICOLOGY SECTION .....</b>	<b>47</b>
A. Introduction.....	47
B. Nonclinical Efficacy Studies.....	48
1. Mechanism of Doxorubicin Action .....	48
2. Effects of DOXIL on Transplantable Tumors in Mice .....	48
3. Summary .....	52

CONFIDENTIAL

DOXIL®  
Liposome Technology, Inc.

Overall NDA Summary  
August 29, 1994

C.	General Pharmacology .....	60
1.	Neurologic Effects .....	60
2.	Cardiovascular Effects .....	60
D.	Nonclinical Absorption, Distribution, Metabolism and Excretion (ADME) Summary .....	64
1.	Introduction .....	64
2.	Plasma Pharmacokinetics .....	65
3.	Tissue Distribution .....	74
4.	Metabolism .....	79
5.	Excretion .....	79
6.	Summary .....	80
E.	Nonclinical Toxicology .....	95
1.	Introduction .....	95
2.	Acute Toxicity Studies .....	96
3.	Repeat Dose Studies .....	97
4.	Special Toxicity Studies .....	101
5.	Reproductive Studies .....	102
6.	Mutagenicity and Genotoxicity Studies .....	103
7.	Summary .....	104
8.	Final Summary .....	123
<b>VI.</b>	<b>HUMAN PHARMACOKINETIC SUMMARY .....</b>	<b>127</b>
A.	Introduction .....	127
B.	Pharmacokinetics of DOXIL (Study 30-14) .....	127
C.	Amount of Non-liposomal Doxorubicin in Plasma .....	129
D.	Comparison of DOXIL Pharmacokinetic Parameters (Study 30-14) to Literature Values for Adriamycin Pharmacokinetic Parameters .....	130
E.	Comparison of DOXIL and DOXIL 1 Pharmacokinetic Parameters (Studies 30-05 and 30-14) .....	131
F.	Doxorubicin Levels in KS Lesions (Studies 30-05 and 30-14) .....	133
<b>VII.</b>	<b>MICROBIOLOGY SUMMARY .....</b>	<b>139</b>
<b>VIII.</b>	<b>CLINICAL DATA SUMMARY .....</b>	<b>140</b>
A.	Introduction .....	140
B.	Clinical Pharmacology .....	142
1.	Clinical Pharmacology/Pharmacokinetics of DOXIL .....	143
2.	Clinical Pharmacology/Pharmacokinetics of DOXIL 1 .....	145
3.	Overall Summary of the Clinical Pharmacokinetics of DOXIL .....	147
C.	Overview of Clinical Studies .....	151

CONFIDENTIAL

DOXIL®  
Liposome Technology, Inc.

Overall NDA Summary  
August 29, 1994

---

D.	Efficacy Studies Supporting Indication .....	153
1.	Methodology: Measuring KS Response .....	154
2.	Efficacy Results .....	157
3.	Discussion of Results from Efficacy Trials .....	165
4.	Efficacy Conclusions .....	166
E.	Safety Summary - General Safety Conclusions.....	169
1.	Primary Database .....	169
2.	Secondary Safety Database.....	186
3.	Clinical Laboratory Data (Chemistry, Hematology, Urinalysis, etc.) .....	187
4.	Clinical Literature Review.....	187
<b>IX.</b>	<b>DISCUSSION OF BENEFIT/RISK RELATIONSHIP AND PROPOSED POSTMARKETING STUDIES.....</b>	<b>191</b>
A.	Patient Population .....	191
B.	Clinical Indication and Patient Profile.....	191
C.	Clinical Benefit .....	192
D.	Risks .....	194
E.	Conclusions.....	197
<b>X.</b>	<b>REFERENCES AND NOTES .....</b>	<b>199</b>

TABLE LEGEND

TABLE 1:	Countries where DOXIL Injection is Available Under Named Patient Sale .....	37
TABLE 2:	Number of Patients Treated by Country Under Named Patient Use Program .....	38
TABLE 3:	DOX-SL Injection Composition .....	40
TABLE 4:	Excipient Quality Standards .....	41
TABLE 5:	DOX-SL Injection Regulatory Specifications .....	43
TABLE 6:	Investigational Formulae .....	45
TABLE 7:	Summary of Clinical Lot Disposition .....	46
TABLE 8:	Summary of DOXIL Formulations used in Nonclinical Studies .....	49
TABLE 9:	Summary Table of Pharmacology Studies of DOXIL .....	54
TABLE 10:	Summary Table of General Pharmacology Studies .....	62
TABLE 11:	Pharmacokinetics of DOXIL in Rats .....	66
TABLE 12:	Mean Pharmacokinetic Parameters of DOXIL and Adriamycin in Rats .....	68
TABLE 13:	Mean Pharmacokinetic Parameters of DOXIL 3 and DOXIL 2 in Rats .....	69
TABLE 14:	Plasma Concentration of Doxorubicin after Treatment with DOXIL or Adriamycin.....	70
TABLE 15:	Tissue AUCs in C26 Tumor-Bearing Mice Treated with DOXIL or Adriamycin.....	74
TABLE 16:	Peak Doxorubicin Concentrations in Tissues of Rats that Received a Single Dose of DOXIL or Adriamycin .....	77

CONFIDENTIAL

DOXIL®  
Liposome Technology, Inc.

Overall NDA Summary  
August 29, 1994

TABLE 17:	Ratio of Tissue Concentrations of Doxorubicin After One or Thirteen Doses of 1 mg/kg DOXIL or Adriamycin.....	78
TABLE 18:	Summary Table of Nonclinical Plasma Pharmacokinetic Studies with DOXIL .....	82
TABLE 19:	Summary Table of Nonclinical Tissue Distribution Studies with DOXIL .....	90
TABLE 20:	Summary Table of Acute Toxicology Studies of DOXIL .....	106
TABLE 21:	Summary Table of Repeat Dose Toxicology Studies of DOXIL .....	108
TABLE 22:	Summary Table of Special Toxicology Studies of DOXIL .....	111
TABLE 23:	Summary Table of Reproductive Toxicology Studies of DOXIL .....	113
TABLE 24:	Summary Table of Mutagenicity Studies of DOXIL.....	114
TABLE 25:	Pharmacokinetic Studies of DOXIL Formulations.....	127
TABLE 26:	DOXIL Pharmacokinetic Parameter Estimates.....	128
TABLE 27:	Summary of Median (range) DOXIL and DOXIL 1 Pharmacokinetic Parameters.....	132
TABLE 28:	Range of Doxorubicin Concentrations in KS Lesions from DOXIL- and DOXIL 1-treated Patients.....	133
TABLE 29:	Concentration of Doxorubicin in KS Lesions and Normal Skin After DOXIL Administration.....	134
TABLE 30:	Predicted Accumulation of Doxorubicin in KS Lesions and Skin Samples .....	135
TABLE 31:	Accumulation Ratio of Doxorubicin in KS Lesions and Skin Samples.....	135
TABLE 32:	Accumulation Ratio of Doxorubicin in KS Lesions and Skin Samples.....	136

CONFIDENTIAL

DOXIL<sup>®</sup>  
Liposome Technology, Inc.

Overall NDA Summary  
August 29, 1994

TABLE 33:	Comparison of Doxorubicin Concentration in KS Lesion After DOXIL 1 or Adriamycin Administration.....	137
TABLE 34:	Overview of DOXIL Clinical Studies Contained in NDA .....	141
TABLE 35:	Summary of DOXIL Formulations used in Clinical Trials .....	142
TABLE 36:	Overview of Open-label, Randomized, Crossover Clinical Pharmacology Studies.....	143
TABLE 37:	Summary of Median (Range) DOXIL and DOXIL 1 Pharmacokinetic Parameters.....	149
TABLE 38:	Overview of Clinical Studies Supporting the Indication .....	153
TABLE 39:	Demographic Summary (KS Patients Only).....	158
TABLE 40:	Best Response and Duration of Partial or Complete Responses.....	160
TABLE 41:	Clinical Benefits by Best Response .....	163
TABLE 42:	Quality of Life Comparison from Study 30-03.....	164
TABLE 43:	Enumeration of Patients Exposed to DOXIL in the Primary Safety Database.....	169
TABLE 44:	Summary of Exposure to DOXIL: Primary Safety Database .....	171
TABLE 45:	Summary of Adverse Events .....	173
TABLE 46:	Summary of Cardiovascular System Adverse Events by COSTART Preferred Term (KS Patients Only).....	182
TABLE 47:	Opportunistic Infections.....	185
TABLE 48:	Enumeration of Patients Exposed (or to be exposed) to DOXIL in Clinical Trials: Secondary Safety Database (Date: May 31, 1994) ...	186
TABLE 49:	Clinical Benefits by Best Response .....	193

FIGURES

FIGURE 1: Diagram of PEG-stabilized "Stealth" Liposome .....33

FIGURE 2: Plasma Concentration of doxorubicin in rats treated with DOXIL. ... 65

FIGURE 3: Plasma concentration of doxorubicin in rats received a single intravenous injection of 4.0 mg/kg DOXIL or DOXIL 1 .....70

FIGURE 4: Plasma concentration of doxorubicin in rabbits treated with single intravenous injection of 1.5 mg/kg DOXIL or Adriamycin .....71

FIGURE 5: Plasma concentration of doxorubicin in dogs that received a single intravenous injection of 1.5 mg/kg DOXIL or DOXIL 1 .....73

FIGURE 6: Concentration of doxorubicin in human prostatic carcinoma xenografts in nude mice treated with 0.9 mg/kg DOXIL or 0.9 mg/kg Adriamycin .....76

FIGURE 7: Plasma Clearance of Adriamycin and DOXIL 1 .....129