CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-388/S-008

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-388/SLR008	**Submission Date:** August 24, 1999
Drug Name:	Navelbine (vinorelbine tartrate)
Formulation:	soft capsules
Sponsor:	Glaxo Wellcome Inc. Five Moore Drive PO Box 13398 Research Triangle Park, NC 27709
Reviewer:	Z. John Duan, Ph.D.
Type of Submission:	Geriatric Labeling Supplement

This is a Clinical Pharmacology and Biopharmaceutics review of a supplemental NDA 20-388, Navelbine (vinorelbine tartrate), for geriatric labeling changes.

SYNOPSIS

Navelbine (vinorelbine tartrate) is a semi-synthetic vinca alkaloid with a modified catharanthine moiety, which causes dissolution of the mitotic spindle apparatus and thus, metaphase arrest in dividing cells.

Navelbine was approved as an intravenous formulation in 1995 for the treatment of non-small-cell lung cancer. Currently, the applicant submitted a geriatric labeling supplement for Navelbine. This review will first briefly summarize the pharmacokinetic characteristics of Navelbine and then evaluate the proposed revisions in Clinical Pharmacology Section.

Pharmacokinetics of intravenous vinorelbine

The following is a brief summary of pharmacokinetics of vinorelbine from the approved package insert.

The pharmacokinetics of vinorelbine were studied in 49 patients who received doses of 30 mg/m^2 in four clinical trials. Doses were administered by 15- to 20-minute constant-rate infusions. Following intravenous administration, vinorelbine concentration in plasma decays in a triphasic manner. The initial rapid decline primarily represents distribution of drug to peripheral compartments followed by metabolism and excretion of the drug during subsequent phases. The prolonged terminal phase is due to relatively slow efflux of vinorelbine from peripheral compartments. The terminal phase half-life

averages 27.7 to 43.6 hours and the mean plasma clearance ranges from 0.97 to 1.26 L/hr per kg. Steady-state volume of distribution (Vss) values range from 25.4 to 40.1 L/kg.

Vinorelbine demonstrated high binding to human platelets and lymphocytes. The free fraction was approximately 0.11 in pooled human plasma over a concentration range of 234 to 1169 ng/mL. The binding to plasma constituents in cancer patients ranged from 79.6% to 91.2%. Vinorelbine binding was not altered in the presence of cisplatin, 5-fluorouracil, or doxorubicin.

Vinorelbine undergoes substantial hepatic elimination in humans, with large amounts recovered in feces after intravenous administration to humans. One metabolite, deacetylvinorelbine, has been shown to possess antitumor activity. This metabolite has been detected, but not quantified, in human plasma. The effects of renal or hepatic dysfunction on the disposition of vinorelbine have not been assessed, but based on experience with other anticancer vinca alkaloids, dose adjustments are recommended for patients with impaired hepatic function.

The disposition of radiolabeled vinorelbine given intravenously was studied in a limited number of patients. Approximately 18% of the administered dose was recovered in the urine and 46% in the feces. Incomplete recovery in humans is consistent with results in animals where recovery is incomplete, even after prolonged sampling times. A separate study of the urinary excretion of vinorelbine using specific chromatographic analytical methodology showed that 10.9% ± 0.7% of a 30-mg/m^2 intravenous dose was excreted unchanged in the urine.

Proposed revisions and rationale

The following additions are proposed in the Clinical Pharmacology Section under pharmacokinetics heading:

Draft

Proposed revisions to the label are based on a summary of the influence of age on the

pharmacokinetics of vinorelbine using data from 3 clinical pharmacology studies (P70-03, PFM-05, and PFM-08) and a published trial.

This analysis was previously submitted to the [redacted] on 11/9/93 in response to a specific request from the FDA Biopharmaceutics reviewer. Complete clinical study reports for these trials were included in the original NDA. On 2/28/1994, the applicant submitted a revised package insert, comments and recommendations regarding this issue from the reviewer were as follows.

"The age-associated changes in the pharmacokinetics of Navelbine was also analyzed (upon request by the Agency) by the sponsor using data from three studies (P70-03, PFM-05, PFM-08). These studies contained a total of 44 cancer patients with age ranging from 41 to 74 years. The ages were normally distributed with a mean value of 57 years. The relationship between age and pharmacokinetic parameters were analyzed by determining the slope and r^2 values using analysis of variance. There were no relationship between clearance, elimination half-life and volume of distribution with age.

"Based on these information the pharmacokinetic section of the labeling should include also the following statement:

Draft

The details of the analysis are presented in **APPENDIX II.**

In addition, in a published study, 25 patients older than 65 years with metastatic breast cancer were treated with vinorelbine 30 mg/m^2 i.v. days I and 8 every 3 weeks; the pharmacokinetics were studied in ten of them. Vinorelbine showed a large apparent volume of distribution (mean 23.4 L/kg), a long terminal half-life (mean 26.2 h) and a large systemic clearance rate (mean 1.2 L/h•kg). These results are similar to those reported in younger patients. No correlation has been found between toxicity, age and drug exposure. This study does not provide a pharmacokinetic rationale for reducing the dosage of vinorelbine in selected elderly patients.

COMMENTS

Based on the comments and recommendations the previous reviewer made and the new information provided, the proposed revisions are acceptable. However, the following changes should be considered.

Draft

DRAFT

The edited version of the above paragraph is as follows.

The influence of age on the pharmacokinetics of vinorelbine was examined using data from 44 cancer patients (average age, 56.7 ± 7.8 years; range, 41 to 74 years; with 12 patients ≥60 years and 6 patients ≥65 years) in 3 studies. CL (the mean plasma clearance), $t_{1/2}$ (the terminal phase half-life), and V_z (the volume of distribution during terminal phase) were independent of age. A separate pharmacokinetic study was conducted in 10 elderly patients with metastatic breast cancer (age range, 66 to 81 years; 3 patients >75 years; normal liver function tests) receiving vinorelbine 30 mg/m^2 intravenously. CL, Vss, and $t_{1/2}$ were similar to those reported for younger adult patients in previous studies. No relationship between age, systemic exposure ($AUC_{0-\infty}$) and hematological toxicity was observed.

RECOMMENDATION

Please convey the Comments to the applicant.

APPEARS THIS WAY
ON ORIGINAL

/S/

Atiqur Rahman, Ph.D. Date

Team Leader
Division of Pharmaceutical Evaluation I

/S/

Z. John Duan, Ph.D. Date

Reviewer
Division of Pharmaceutical Evaluation I

CC: NDA 20-388 original
HFD-150 Division File
HFD-150 MPelosi
HFD-150 SHonig
HFD-850 LLesko
HFD-860 MMehta, ARahman, JDuan
CDR

TABLE OF CONTENTS

SYNOPSIS 1

Pharmacokinetics of intravenous vinorelbine 1

Proposed revisions and rationale 2

COMMENTS 3

RECOMMENDATION 4

TABLE OF CONTENTS 6

APPENDIX I DRAFT LABELING 7

APPENDIX II. ANALYSIS OF AGE-ASSOCIATED CHANGES IN THE PHARMACOKINETICS OF NAVELBINE. 21

14 pages redacted from this section of the approval package consisted of draft labeling

DRAFT

LABELING

APPENDIX II. Analysis of age-associated changes in the pharmacokinetics of NAVELBINE.

Three studies (P70-03, PFM-05, PFM-08) were used for this analysis. Patient specific data are presented in the following table. These studies contained a total of 44 cancer patients. The age distribution of these patients is presented in Figure 3.1, The average age was 56.7 ± 7.8 years (mean ± SD) and the range was 41 to 74 years. As shown in the figure, the ages were normally distributed.

The relationships between age and clearance, half-life and volume of distribution were explored by regression analysis. All analyses were performed using the SAS System for Windows (Release 6.08).

Figure 3.2 contains a plot of vinorelbine clearance versus age, results of analysis of

variance, parameter estimates, and a summary of the fit. There was no relationship between vinorelbine clearance and age as evidenced by the estimate of the slope of 0.0009 (p=0.9157) and r^2 value of 0.0003.

Figure 3.3 contains a plot of vinorelbine half-life versus age. Again, there was no evidence of a correlation between vinorelbine half-life and age as evidenced by a slope of 0.1073 (p=0.7821) and r^2 value of 0.0018.

Figure 3.4 contains a plot of vinorelbine V_{beta} versus age for patients from the 2 studies (PFM-05, PFM-08) in which V_{beta} was determined (only Vss was estimated in the study of Lucas, et al., P70-03). As with clearance and half-life, there was no evidence of a correlation between vinorelbine V_{beta} and age as evidenced by a slope of -0.5868 (p=0.5621) and r^2 value of 0.0131.

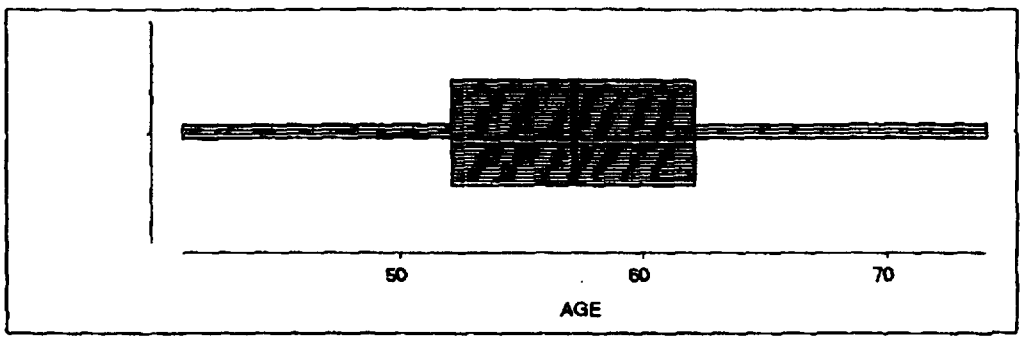
Consequently, in this group of 44 patients, there was no evidence of an age-dependency For the pharmacokinetics of vinorelbine.

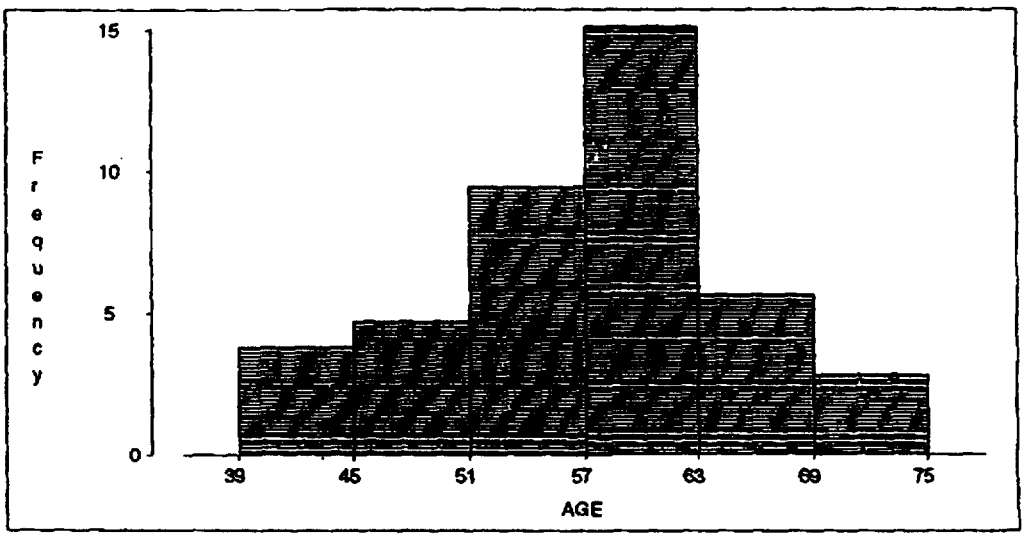
Study Number	Patient ID	Gender	Age	CL (L/hr/kg)	$t_{1/2}$ (hr)	V^a (L/kg)
PFM-05	1	M	66			
	2	M	53			
	3	M	64			
	4	M	74			
	5	M	51			
	6	M	57			
	7	M	59			
	8	M	53			
PFM-08	1	M	50			
	2	M	66			
	3	M	59			
	4	M	59			
	5	M	49			
	6	F	41			
	7	M	62			
	8	M	62			
	9	M	64			
	10	M	63			
	11	M	57			
	12	M	59			
	13	M	74			
	14	M	68			
	15	M	59			
	16	M	46			
	17	M	58			
	18	M	57			
	19	M	48			
	20	M	70			
P70-03	201	F	44			
	202	F	52			
	203	M	54			
	204	M	54			
	205	F	43			
	206	F	53			
	207	M	44			
	208	F	54			
	209	M	48			
	211	F	57			
	212	F	58			
	213	F	56			
	214	F	52			
	215	F	57			
	216	F	59			
	219	M	62			

[a] Volume of distribution tabulated as V_b for PFM-05 and PFM-08 and as V_{ss} for P70-03. V_{ss} was not calculated for PFM-08 and V_b was not calculated for P70-03.

Figure 3.1 **Age Distribution of Patients (n=44)**

AGE

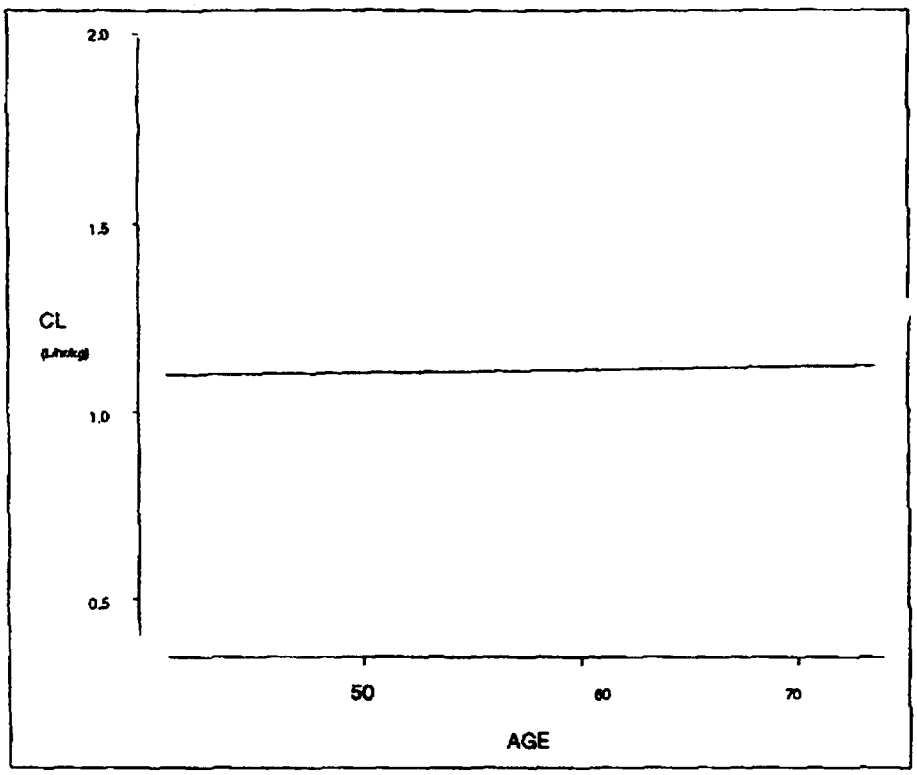




Moments			
N	44.0000	Sum Wgts	44.0000
Mean	56.7045	Sum	2495.0000
Std Dev	7.7896	Variance	60.6781
Skewness	0.1461	Kurtosis	-0.0815
USS	144087.000	CSS	2609.1591
CV	13.7372	Std Mean	1.1743

Quantiles					
100% Max		99%	74.0000	Range	
75% Q3	62.0000	95%	70.0000	Q3-Q1	10.0000
50% Med	57.0000	90%	66.0000	Mode	59.0000
25% Q1	52.0000	10%	46.0000		
0% Min		5%	44.0000		
		1%	41.0000		

Figure 3.2 **Relationship Between Clearance and Age for Vinorelbine**



Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Stat	Prob > F
Model	1	0.0019	0.0019	0.0113	0.9157
Error	42	7.2084	0.1716		
Total	43	7.2104			

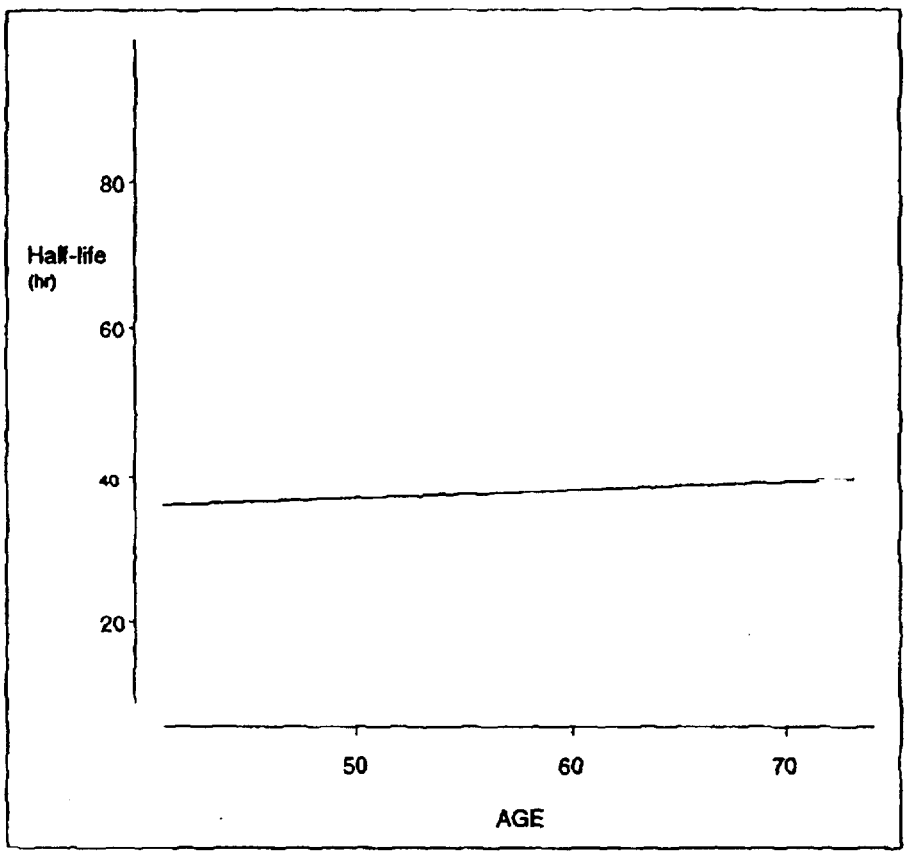
Parameter Estimates

Variable	DF	Estimate	Std Dev	T Stat	Prob > |T|
Intercept	1	1.0606	0.4641	2.2851	0.0274
Infrate	1	0.0009	0.0081	0.1065	0.9157

Summary of Fit

Mean of Response	1.1095	R-Square	0.0003
Root MSE	0.4143	Adj R-Sq	0.0

Figure 3.3 **Relationship Between Half-life and Age for Vinorelbine**



Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Stat	Prob > F
Model	1	30.0451	30.0451	0.0775	0.7821
Error	42	16278.7904	387.5902		
Total	43	16308.8355			

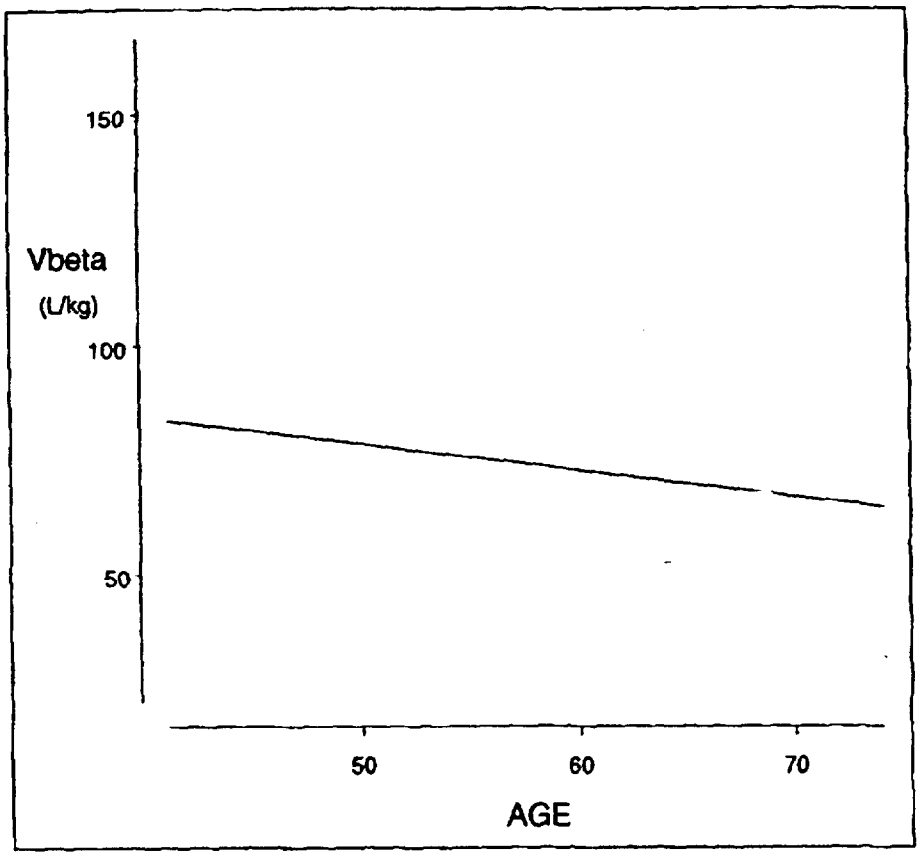
Parameter Estimates

Variable	DF	Estimate	Std Dev	T Stat	Prob > |T|
Intercept	1	31.0833	22.0558	1.4093	0.1661
Infrate	1	0.1073	0.3854	0.2784	0.7821

Summary of Fit

Mean of Response	37.1682	R-Square	0.0018
Root MSE	19.6873	Adj R-Sq	0.0

Figure 3.4 **Relationship Between V_{beta} and Age for Vinorelbine**



Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Stat	Prob > F
Model	1	612.0018	612.0018	0.3448	0.5621
Error	26	46150.4593	1775.0177		
Total	27	46762.4611			

Parameter Estimates

Variable	DF	Estimate	Std Dev	T Stat	Prob > |T|
Intercept	1	107.3687	59.3537	1.8090	0.0820
Infrate	1	-0.5868	0.9993	-0.5872	0.5621

Summary of Fit

Mean of Response	72.8321	R-Square	0.0131
Root MSE	42.1310	Adj R-Sq	0.0

[1] Jehl F, Quoix E, Leveque D, et al. Pharmacokinetics and preliminary metabolic fate of Navelbine in humans as determined by high performance liquid chromatography. *Cancer Res.* 1991;51:2073-2076.

[2] Marquet P, Lachatre G, Debord J, et al. Pharmacokinetics of vinorelbine in man. *Eur J Clin Pharmacol.* 1992;42:545-547.

[3] Lucas S, Donehower R, Rowinsky E, et al. Absolute bioavailability and pharmacokinetics of weekly Navelbine liquid-filled soft gelatin capsules at full therapeutic doses in patients with solid tumors. *Ann Oncol.* 1992;3(suppl 1):125.

[4] Sorio R, Robieux I, Galligioni E et al. Pharmacokinetics and tolerance of vinorelbine in elderly patients with metastatic breast cancer. *Eur J Cancer.*1997;33(2):301-303.

[5] The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small cell lung cancer. *J National Cancer Institute.* 1999;91(1):66-72.

[6] The Elderly Lung Cancer Vinorelbine Italian Study Group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non-small cell lung cancer. *J National Cancer Institute.* 1999;91(1):66-72.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-388/S-008

Administrative Documents