CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-388/S-008

Approval Letter

NDA 20-388/S-008

Glaxo Wellcome INC
P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Marna Doucette
Product Director, Regulatory Affairs

Dear Ms. Doucette::

Please refer to your supplemental new drug application dated August 24, 1999, received August 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Navelbine (vinorelbine) for Injection.

This supplement proposed changes to the CLINICAL PHARMACOLOGY: Pharmacokinetics, CLINICAL PHARMACOLOGY: Clinical Trials, and ADVERSE REACTIONS: Hematologic subsections and was submitted pursuant to 21 CFR 314.70 requiring a Geriatric Use subsection for prescription drug labeling

We also acknowledge receipt of your April 11, 2000 amendment that provides for a complete response to our February 28, 2000 not approvable letter.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-388/S-008." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Maureen Pelosi, Project Manager, at (301) 594-5778.

Sincerely,

/S/

Robert L. Justice, M.D.
Deputy Director
Division of Oncologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 20-388
HFD-150/Div. Files
HFD-150/M.Pelosi
HFD-150/Susan Honig/
Grant Williams/
John Duan/
Atik Rahman/

HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-101/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: MP/May 15, 2000
Initialed by: Pease/
final:Pelosi/5-15-00

filename: My Documents/NDA/20388_008

APPROVAL (AP)

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Five Moore Drive
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Attention: Marna Doucette
Product Director, Regulatory Affairs

Dear Ms Doucette:

Please refer to your supplemental new drug application dated August 24, 1999, received August 30, 1999, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act for Navelbine (vinorelbine tartrate) Injection.

This supplement proposes changes to the CLINICAL PHARMACOLOGY: Pharmacokinetics, CINICAL PHARMACOLOGY: Clinical Trials, and ADVERSE REACTIONS: Hematologic subsections and was submitted pursuant to 21 CFR 314.70 requiring a Geriatric Use subsection for prescription drug labeling.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

1. **CLINICAL PHARMACOLOGY: Clinical trials (page 5)**

Draft

Please remove the above paragraph from the label. In the Clinical Trials section, it is customary to include information from trials reviewed by the Division and data used to make the approval decision. Information about the ELVIS trial is derived from a

publication without review of primary data. The trial design was flawed and the information provided in the publication does not permit any conclusions about QOL or specific toxicity related to vinorelbine. The fact that 20% of patients stopped treatment because of toxicity or choice does not support the final statement.

2. Geriatric Use subsection (page 8):

The underlined sections are the new proposed labeling:

DRAFT

a. The addition of the phrase ". [redacted] ' is not warranted. The Guidance defines geriatric as age 65 or greater. You did not provide any information relevant to safety and efficacy in the population aged 75 or older. Specific analyses and primary data are needed to support these claims.

b. Please delete the two new sentences beginning with [redacted]. Based on the limitations of this study's design and the data reported in the publication, the existing sentence ("Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.") best describes the available information.

3. Adverse Reactions, Hematologic (page 10):

[redacted]

a. Please remove the proposed revisions. The reported toxicities occurred in a trial with a vinorelbine schedule that differs from that of approved labeling and other reported clinical trials. The second sentence makes a comparative

claim based on a small number of patients with a high drop-out rate in a study

that was halted early because of poor accrual.

b. This information is misleading, as not all adverse events from the trial were included in the organ-specific adverse event labeling. For example, the approved labeling lists an overall incidence of constipation, any grade, as 35% for all patients and 29% in NSCLC patients (Table 1). In the ELVIS study, there was a 52% incidence of constipation of any grade. Similarly, there was a 20% incidence of vomiting (any grade) in the single-agent trial described in the label in Table 1, compared to 32% in the ELVIS study. The incidence of some adverse events was higher in the ELVIS study and the incidence of other adverse events lower in the ELVIS study compared to the reviewed, labeled trials. However, the quality of the available data from the ELVIS study does not permit comparative analyses, and specifics from this trial should not be cited in the label.

Additionally, we have the following comments:

1. The addition of the word "adult" in the "Geriatric Use" subsection is appropriate as it delineates an adult from a pediatric population.

2. **Clinical Pharmacology, Pharmacokinetics (page 3):**

DRAFT

The proposed revisions are acceptable however, please consider the following changes:

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, V_{ss}, 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.

3. You may wish to consider submission of primary data from this trial for review. Many of the enclosed comments result from lack of information in the published report, which might be addressed with review of a complete dataset.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Maureen Pelosi, Project Manager, at (301) 594-5778.

Sincerely,

Robert L. Justice, M.D.
Deputy Director
Division of Oncologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-388 /S-008
HFD-150/Div. Files
HFD-150/ M.Pelosi
HFD-150/ S. Honigs/2-15-00
G. Williams/2-15-00
J. Duan/AR for 2/11/00
A. Rahman/2/11/00
HFD-810/DNDC Division Director
DISTRICT OFFICE

Drafted by: map/1-24-00, revised 2-16-00
Initialed by:Pease/2-2-00
Revised draft initialed by Pease/ 2-17-00
Final: by Pelosi/ 2-17-00
Initialed by Pease:

filename: 20388NA2_008.doc

NOT APPROVABLE (NA)

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