

April 15, 1999

We are reviewing your submission and have identified the following comments and information requests:

1. In study HEPI 013, you calculated relative dose-intensity. Please describe this calculation in detail, since patients could have received from 6-9 cycles per protocol.
2. For study HEPI 013, volume 2.33, page 8/24/048 indicates that 223 patients on FEC and 231 on CMF were included in the analysis of TTF. Figure 3, page 8/24/132 shows that the total patients included in the Kaplan-Meier curve were 220 and 231 respectively. There is a small discrepancy between the numbers of patients included in the survival curve also. Are these differences due to early drop-out? Please explain the discrepancies.
3. Review of the line listings for cardiac toxicity (volume 2.37, listing 8.2) for study HEPI 013 showed symptoms in 2 patients on CMF and 8 patients on FEC that could be consistent with cardiac dysfunction:

FEC:

Patient 5-62 AR: Paroxysmal nocturnal dyspnea and tachycardia; occurred after treatment was discontinued

Patient 11-29 IT: Tachycardia, dyspnea after C1

Patient 13-1 GR: Angina after C3

Patient 24-62 IT: DOE after C2

Patient 26-13 DD: DOE and tachycardia at C3

Patient 34-13 URSS: Peripheral edema, tachycardia at C5

Patient 52-3 CS: Shortness of breath, DOE, edema, and tachycardia after C4

Patient 56-21 PL: SOB, DOE, cough, tachycardia after C4

CMF:

Patient 26-2: DOE, nocturia, tachycardia after C1

Patient 49-11: Peripheral edema

Did these patients have other reasons for these symptoms? Please explain why they were not included in the discussions of cardiac toxicity.

4. Queries of the electronic database showed 4 patients with CHF on FEC who were not discussed in the study report. These patients are:
5-29
13-5
23-11
58-24

Please supply narratives for these patients.

5. In the electronic database for HEPI013, data on survival was entered for 429 patients, not for the 460 randomized patients (Table FOLSTAT). Why were 31 patients excluded from this table? Please supply the date of death and the censor date for all patients. (Censor status is available from table EFFICACY).
6. Please define how TTP was censored. Did you use the last date the patient was seen, the last date the patient was fully evaluated, or the last date there was any contact with the patient (i.e., by phone), or some other method?
7. In study HEPI 013, it is not clear to me how many patients were observed without further therapy, for how long, and whether progression occurred on or off treatment. Please indicate how many patients received all 6 cycles, and how many at that point were responders (CR +PR) and how many had no change. Of the patients with no change, how many were observed? Average length of observation? Did progression occur off therapy? Any difference between treatment arms? Please provide the same information for responders-- how many received 3 additional cycles of treatment, how many were observed instead, average length of observation, progression on or off chemotherapy, differences between treatment arms.
8. In study HEPI 013, "pain on injection" was recorded in the database table "AES" but no grades are recorded. "Extravasation" is treated the same way, yet at least one patient, according to the narratives (patient on FEC listed as "thrombophlebitis"). How many patients experienced these problems? Were other extravasations recorded, and what medical intervention did they require?
9. Febrile neutropenia is listed as a symptom in the AE database table for advanced breast cancer, but no grades are listed. Please supply documentation of which patients experienced febrile neutropenia.
10. For study HEPI 013, you reported grade 3-4 neutropenia in 171 patients on FEC and in 156 patients on CMF. A database query for neutrophils less than 1000 reports 187 patients on FEC and 189 on CMF with grade 3-4 neutropenia. Did you use different grading criteria?

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If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

MESSAGE CONFIRMATION

04/28/99 12:36

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
04/28	01'42"	616 833 0409	CALLING	04	OK 0000

04/28/99

12:33

NO. 183

001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. We remind you that we are still awaiting a response to the comments and information requests that were sent via facsimile transmission on March 25, 1999 and April 15, 1999. I have attached those comments and information requests for your convenience. If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

Date: April 28, 1999

Total number of pages, including cover sheet 4

Phone: (301) 594-5767

FROM: Patrick F. Guinn, CSO/Project Manager

Fax: (616) 833-0409

TO: Denise Tindel (616) 833-3825

PHONE: (301) 594-2473 FAX: (301) 594-0498

document to the addressee, you are hereby notified that any further dissemination of this document is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: April 28, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

*cc: Orig NDA 21-010
Div File
P. Guinn*

We are reviewing your submission and have identified the following comments and information requests:

- Please provide the following information:

How many of each, relapses and deaths, occurred after the interim analysis but before the final analysis for study MA5? Please present this as a frequency and as a proportion of the total number of relapses and deaths.

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TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 3

Date: April 15, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.
IR #8

*cc= Orig NDA 21-010
Div File
SHonig
RGuinn*

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MESSAGE CONFIRMATION

04/15/99 14:02

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
04/15	01'15"	616 833 0409	CALLING	03	OK 0000

04/15/99 14:00

NO. 134 001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

Date: April 15, 1999

Total number of pages, including cover sheet 3

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

PHONE: (301) 594-2473 FAX: (301) 594-0498

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Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: April 7, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

*cc = Orig NDA 21-010
Dir File
SKim
~~PGuinn~~*

We are reviewing your submission and have identified the following comments and information requests:

- Regarding primary stability data for the drug product, it is noted that one month stability data were submitted in the pending NDA 21-010. Please update the primary stability data (e.g. long-term and short-term data) as soon as possible. It is expected to submit up to 6 month stability data at this time followed by updating up to 9 month by the end of May, 1999. Please note that the submitted data in the original application are not enough to assess the proposed expiration dating period of _____ at this time.

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Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: April 7, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

NO. 090 001

04/07/99 08:43

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
04/07	00:44"	616 833 0409	CALLING	02	OK

04/07/99 08:44

MESSAGE CONFIRMATION

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TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: March 25, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

*Orig NDA 21-010
Div File
S Honig
~~DC~~*

We are reviewing your submission and have identified the following comments and information requests:

1. Investigative groups have attempted to define a set of anthracycline doses that are "equivalent" to certain doses of doxorubicin. Do you have a defined "equivalence set" for epirubicin and doxorubicin? For example, what dose of epirubicin do you feel is comparable to doxorubicin doses of 300 mg/m² and 450 mg/m²?
2. Were serotonin receptor antagonist drugs, such as ondansetron and granisetron, used in HEPI013?
3. I previously asked a question about randomization in study GFEA-05 (FDA fax 2/26/99). In your response dated 3/5/99, you stated for question 4 that "...the randomization was not stratified, at variance with what was stated in the protocol." Does this mean that randomization was not stratified by center, was not stratified by nodal status, or was not stratified in any way? Please clarify this statement, and explain why stratification did not occur.
4. What is the data lock date for protocol HEPI 013?
5. Where is the analysis of quality of life for HEPI 013?

In response to the submission dated 3/22/99 from Pharmacia & Upjohn:

In the FDA fax dated 3/5/99, question 5 states "In studies MA-5 and GFEA-055, was CT treatment planning used at all investigative sites when irradiating left sided lesions?"

- Yes, CT stands for computerized tomography. My question concerns any possible contribution of radiation therapy as part of the local treatment for a left-sided breast cancer to observed cardiotoxicity. If CT treatment planning is used, a minimal amount of heart is included in the field. If CT scans are not used, cardiac exposure to radiation increases and can increase the risk for cardiomyopathy. Please do not re-examine each case individually. A general feeling for whether or not CT planning was used by most radiation oncologists at most centers will suffice. We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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MESSAGE CONFIRMATION

03/25/99 15:07

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
03/25	00'54"	616 833 0409	CALLING	02	OK 0000

03/25/99 15:05

NO. 044 001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

Date: March 25, 1999

Total number of pages, including cover sheet 2

Phone: (301) 594-5767

FROM: Patrick F. Guinn, CSO/Project Manager

Fax: (616) 833-0409

TO: Denise Tindel (616) 833-3825

PHONE: (301) 594-2473 FAX: (301) 594-0498

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Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 3

Date: March 25, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.
Questions #4

*cc: Orig NDA 21-010
Div File
S Monig
P. Guinn*

We are reviewing your submission and have identified the following comments and information requests:

1. In volume 2.29, page 8/20/317, the first narrative refers to the drug "isoprenaline." Please clarify the nature of this drug--it is not listed/manufactured in the United States. Is it isuprel?
2. In protocol MA-5, one of the sites was Hospital St. Luc. Was  one of the associate investigators at this site? Did he enter any patients on the trial?
3. In protocol MA-5, premenopausal women were analyzed separately from perimenopausal women as exploratory subset analyses. What definitions were used to distinguish pre- and perimenopausal status?
4. Did you include the investigator's term for adverse events in the database? For example, in study MA-5, I am trying to locate the actual description by the investigator that corresponds to the cardiovascular AE categories of "function", "pain", "dysrhythmia", "edema", and "venous."
5. According to the MA-5 protocol, MUGA scans were used to determine cardiac function, but ECHO could be used if the center did not have nuclear medicine capabilities. From the FDA.CARVAS database, it appears that all centers used MUGA scans throughout the study, and no one was tested for LVEF with an ECHO. Is this statement correct?
6. According to the MA-5 protocol, patients with clinical T1-3 were eligible. Patients with pathologic evidence of dermal lymphatic invasion were still eligible, provided that there was no clinical evidence of inflammatory breast cancer prior to surgery. How many patients had dermal lymphatic invasion seen at path? This information is not included in the database.
7. Please provide electronically the number of involved nodes found for each patient in studies MA-5 and GFEA-5. This information was not coded in the database.
8. How many patients entered study MA-5 with bilateral breast cancer? How many had unilateral versus bilateral axillary node dissections? What was the pathologic staging for each cancer in these patients? This information is not provided in the electronic database.
9. In MA-5, how many women had positive margins after lumpectomy and did not undergo re-excision? This information is not in the database.
10. Please identify the 6 patients on MA-5 who received concurrent radiation therapy and chemotherapy. From my database queries, I think the patients on the CEF arm are patients MG2 and PN1.

For CMF, all of the following patients appear to have overlapped radiation and chemotherapy treatments:

CENTER	PATID
GS	3
HO	6
KG	2
LM	77
MN	21
MN	27
MP	3
MP	9
MV	4
SA	2
SS	27

Which patients were considered to have received concurrent treatment in your analysis? Were some patients excluded because they started radiation during the second half of C6 (i.e., before the official end of therapy, but after all drugs were administered on days 1-14)?

Is this correct? Please provide the reasons for dose reductions in these patients.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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MESSAGE CONFIRMATION

03/25/99 08:29

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
03/25	01'08"	616 833 0409	CALLING	03	OK 0000

03/25/99

08:27

NO. 038 001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

Date: March 25, 1999

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FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: March 11, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached request for additional desk copies.

*cc: Orig NDA 21-010
Div File
~~Reprint~~*

We are reviewing your submission and have identified the following items that are needed as additional desk copies:

1. Please provide an additional electronic copy of the 2 diskettes that were provided in your submission dated March 5, 1999. These 2 diskettes included CARVAS.SD2, CARVAS.PDF, and CARVAS.MDB
2. Please provide an additional electronic version of the CD sent with your submission dated March 2, 1999.

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MESSAGE CONFIRMATION

03/11/99 16:55

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
03/11	00'44"	616 833 0409	CALLING	02	OK 0000

03/11/99 16:54

NO. 210 001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached request for additional desk copies.

Date: March 11, 1999

Total number of pages, including cover sheet 2

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

PHONE: (301) 594-2473 FAX: (301) 594-0498

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 3

Date: March 5, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request. #6

cc: Orig NDA 21-010
Div File
S Monig
PK

We are reviewing your submission and have identified the following comments and information requests:

1. In the Periodic Report of Adverse Events submitted to IND (N 238), it is stated that one report for "exposure in utero" was received. Is this the only report in the company files of epirubicin use during pregnancy?
2. In the same periodic report, there are several different areas where reports of leukemia are described:
 - On page 9, it is stated that 4 cases of acute leukemia were identified in patients treated with intra-arterial epirubicin.
 - On page 20, Table 9 summarizes reported cases by leukemia subtype during the reporting period 7/1/93 to 6/30/98 (28 AML/MDS).
 - On page 27, 9 secondary leukemias were reported during 1993-8 on the NDA pivotal/supportive trials.
 - On page 29, 4 cases of leukemia were reported as "late-breaking information", from July 1 to October 20, 1998. Two of these cases may have been included in the listings on page 27.
 - On page 33, 3 cases of leukemia were reported between 1/1/90 and 6/30/99.

How many unique cases of leukemia exist in the database, either through spontaneous reporting or clinical trial monitoring?

3. Thank you for your response of 2/25/99 to question 7. However, in Table 11 volume 2.19 page 76, the number of deaths in the "Off therapy" column totals 85, not 86. You mention in your answer that the cause of death in patient KG003 was unknown; I presume she is the missing patient from this table. Is this correct? Please supply the narrative for this patient.
4. The submitted CRFS were for "death, dropouts due to AE, leukemia, and cardiac toxicity." CRFs on all leukemia patients in studies MA-5 and GFEA-05 were submitted. However, only about half of patients listed with cardiac toxicity on study GFEA-05 had their CRFs submitted. Please explain the selection process for CRF submission.
5. In studies MA-5 and GFEA-05, was CT treatment planning used at all investigative sites when irradiating left-sided lesions?
6. In table 6, volume 2.28, page 42, you list the number of patients who did not complete chemotherapy and the reasons for study GFEA-05. However, an Access query of the database (Summary table; Reason) indicated that 20 patients on FEC 100 and 18 on FEC 50

withdrew early, rather than the 16 and 14 patients you reported in the table. The reasons for withdrawal were different also:

- FEC 50: 7 for toxicity
 2 death
 5 patient refusal
 3 other
 1 unknown

- FEC 100: 1 disease progression
 12 toxicity
 1 death
 3 patient refusal
 3 other

Please explain the discrepancy between the reported table and the database tabulations.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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03/05/99 15:44

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
03/05	01:05"	616 833 0409	CALLING	03	OK 0000

03/05/99 15:42

NO. 181 001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

Date: March 5, 1999

Total number of pages, including cover sheet 3

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

PHONE: (301) 594-2473 FAX: (301) 594-0498

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TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: March 4, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

*CC: Orig NDA 21-010
Div File
S. Honig
S. Ibrahim
~~PC~~*

We are reviewing your submission and have identified the following comments and information requests:

1. Please provide an additional copy of Volume 1.25.
2. Please provide an additional desk copy of Amendment 001 submitted February 12, 1999.
3. Please provide an additional desk copy of Amendment 004 submitted February 25, 1999.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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03/04/99 10:54

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
03/04	00:44"	616 833 0409	CALLING	02	OK 0000

03/04/99 10:52

NO. 160 001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

Date: March 4, 1999

Total number of pages, including cover sheet 2

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

PHONE: (301)594-2473 FAX: (301) 594-0498

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TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 3

Date: February 26, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

cc: Orig NDA 21-010
Dir File
S Honig
P Guinn

We are reviewing your submission and have identified the following comments and information requests:

1. In the Early Breast Cancer dataset, table Endpoints contains the field "DDC." This field should contain the date of death, but instead contains a string of numbers. When converted to date/time format from numeric format, the dates appear to correspond with the date of death plus 60 years plus 1 day. For example, patient AJ4 died 1/12/97. The Endpoint table contains the entry 13526; it converts to a date of 1/11/37. Please explain how these entries were created. Is the correction factor that I used correct?

2. In my review of the electronic CRFs:
Patient EJ2 is listed with a death date of 3/7/97.
Patient MP21 is listed with a death date of 3/25/97.
Patient SA16 is listed with a death date of 2/20/97.

Patient MX16 is listed with a death date of 2/24/98.
Patient PS9 is listed with a death date of 2/8/98.
Patient SA8 is listed with a death date of 10/5/97.

All are listed as alive in the Endpoints table. The last 3 deaths occurred after the data lock date of 5/15/97, but the first 3 should have been entered.

Patient MJ2 is listed with a death date of 10/29/96, but is listed in the database as dying on 12/29/96.

Patient NW 14 is listed in two places in the CRF with a death date of 9/25/95; she is listed in the database with a death date of 9/29/95.

Please explain these discrepancies and recalculate the survival rates.

3. A CRF for patient MV18 was submitted; this patient does not appear in the database. Is this really patient MU18?
4. In the study report for GFEA-05, volume 2.28, page 8/19/023, section 4.2.3: the statement "the protocol-specified randomization procedure was not reflected in the randomization list" appears. What does this statement mean?
5. I reviewed the randomization logs for GFEA-05; they do not include the date the patient was randomized. Was this information inadvertently excluded from the submission?

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

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PHONE: (301)594-2473 FAX: (301) 594-0498

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 3

Date: February 26, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

NO. 137 12:42 02/26/99

0000 OK 03 CALLING 616 833 0409 01'00" 02/26
DATE S-R-TIME DISTANT STATION ID MODE PAGES RESULT

02/26/99 12:44

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TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: February 17, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

*Orig NDA 21-010
Div File
Guinn
Stonig*

We are reviewing your submission and have identified the following comments and information requests:

1. Protocol GFEA 05 was amended 11/20/90. Was the only change to the protocol the change in the tumor grade (from 3 to 2 or 3)? How many women had been accrued to the trial when the change was made?
2. In protocol GFEA 05, the target sample size was 592 evaluable patients. Accrual was stopped after 565 patients were randomized. Please explain why the original sample size was not used.
3. In study GFEA 05, was postmastectomy chest wall irradiation permitted?
4. Why was an unplanned interim analysis performed after 3 years on study GFEA 05?
5. What were the accrual dates for study GFEA 05? Accrual began April 10, 1990, but I cannot find the closing date for accrual.
6. On study GFEA 05, were the following adjunctive therapies used: colony stimulating factors, prophylactic antibiotics, serotonin selective antiemetic agents such as ondansetron?
7. In volume 2.28 on page 8/19/178, listing 7.1.1.2: are the cumulative anthracycline doses for metastatic disease calculated separately from the cumulative epirubicin dose, or do they include the adjuvant dose? For example, Pt A074: Does the cumulative metastatic dose of epi = 550 include the adjuvant dose of 292.7, or is it calculated in addition to the adjuvant dose for a total epi dose in this patient of 842.7? For patient L016, the doxorubicin cumulative dose for metastatic disease is 675 mg/m². Did she receive this dose of doxorubicin in addition to 318.4 mg/m² of epirubicin, or have you converted the epirubicin dose to a doxorubicin equivalent, and added it to the actual dox dose?

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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02/17/99 11:31

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
02/17	00'52"	616 833 0409	CALLING	02	OK 0000

02/17/99 11:29

NO. 066 001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

Date: February 17, 1999

Total number of pages, including cover sheet 2

Phone: (301) 594-5767

FROM: Patrick F. Guinn, CSO/Project Manager

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TO: Denise Tindel (616) 833-3825

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FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: February 17, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

*cc: Orig NDA 21-010
Div File
S Monig
~~PK~~*

We are reviewing your submission and have identified the following comments and information requests:

The EBC database for NDA 21010 contains an error in data set FDA.CARVAS. The variable "MUGADT" should give the date the MUGA scan was performed in study MA-5. In both the SAS and Access versions, this date ranges from 1/1/60 to 1/7/60. Please correct this problem and send us the updated data set as soon as possible.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

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02/17/99 11:45

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
02/17	00'44"	616 833 0409	CALLING	02	OK 0000

02/17/99 11:44

NO. 068 101

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

Date: February 17, 1999

Total number of pages, including cover sheet 2

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Phone: (301) 594-5767

TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

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TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 3

Date: February 5, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

*cc = Orig NDA 21-010
Div File
PGuinn*

Medical Comment:

It would help facilitate the review of this NDA if an electronic copy of the study reports of the pivotal and supportive trials for each indication was provided.

Information Requested January 29, 1999:

1. You have included the protocol document for Study MA5, which indicates that the study was amended on May 17, 1990 and on October 18, 1990. Please provide the actual amendments; what aspect of the protocol was changed?
2. How was the Breast Cancer Chemotherapy Questionnaire in study MA5 scored? The protocol defined a change of 0.5 as clinically significant, but did not outline how the individual questions were used to generate a score.
3. Please provide us with an additional copy of volume 2.8.

Additional Information Request:

1. In volume 2.20 page 8 11 025, the schedule of evaluations indicated that the BCQ should be performed at the 6 month visit (Study MA-5). In volume 2.19 page 8 10 042, the schedule of evaluations does not show that the BCQ was obtained at 6 months. Please clarify at which timepoints the BCQ was obtained.
2. Volume 2,20, page 49 indicates that two questions were added to the BCQ (Study MA-5). Please specify which questions were added, when these questions were added, how many patients were on study when the questionnaire was changed, and what the median follow-up was at the time of the amendment.
3. Does the database include the number of patients who required blood and platelet transfusions, and how many times/units they required?
4. I noted that the CRF for study MA-5 collected information on patients who used a cooling cap. Was this information entered in the database? If so, where is it located?
5. Table 2.1, volume 2.19, page 99 lists the following protocol violations: "Quality of life, Therapeutic: Modification, and Therapeutic: REgimen." Please define these protocol violations.
6. Dose modifications are outlined in the protocol. Do these modifications refer to reductions in all 3 drugs in the treatment regimen?
7. Table 11 page 76, volume 2.19 shows the numbers of non-breast cancer-related deaths. Two patients are reported to have died of a combination of disease and non-protocol therapy. Four

patients are reported to have died of "other" causes. In volume 2.22, pages 29-30 contain the narratives for "deaths not breast cancer" and "disease and non-protocol treatment". While there are 4 and 2 narratives in these sections respectively, patient KO 003 is listed twice. Was her death counted in both categories? Is this double listing an error? If so, there should be one additional death narrative for a CEF patient. Also, there is no death narrative for the patient on CMF who died of "other" causes. Please clarify.

8. The three year study report, in volume 2.26 page 8/17/197, states that 2 patients died on study and that 3 patients experienced disease progression (section 7.2.2). The current report states that 1 patient died on study and that 2 patients experienced disease progression. Please explain the differences in the two reports.
9. The 3 year study report (vol. 2.26 page 8/17/203) states that 50 patients on CEF and 31 on CMF had LVEF that dropped below 50%. In volume 2.19, page 83, Table 16 shows the number of abnormal MUGA scans obtained over time. This table appears to show that 32 patients on CEF and 11 on CMF had abnormal scans. Please explain the difference in these two sets of numbers.
10. The 3 year report also contains the hospitalization rates for each arm (page 8/17/204). These figures should be accurate, since the report was written after all patients had been accrued and had finished therapy. Do you have a list of the reasons for hospitalization, or can you direct me to its location in the electronic database?

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MESSAGE CONFIRMATION

02/05/99 15:23

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
02/05	01'06"	616 833 0409	CALLING	03	OK 0000

02/05/99 15:21

NO. 019 001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

Date: February 5, 1999

Total number of pages, including cover sheet 3

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

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TO: Denise Tindel (616) 833-3825
Fax: (616) 833-0409

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 2

Date: January 29, 1999

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

Information Request:

1. You have included the protocol document for Study MA5, which indicates that the study was amended on May 17, 1990 and on October 18, 1990. Please provide the actual amendments; what aspect of the protocol was changed?
2. How was the Breast Cancer Chemotherapy Questionnaire in study MA5 scored? The protocol defined a change of 0.5 as clinically significant, but did not outline how the individual questions were used to generate a score.
3. Please provide us with an additional copy of volume 2.8.

**APPEARS THIS WAY
ON ORIGINAL**

MESSAGE CONFIRMATION

02/01/99 14:13

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
02/01	00'38"	616 833 0409	CALLING	02	OK 0000

02/01/99 14:12

NO.007 001

COMMENTS: Please refer to your NDA 21-010 regarding epirubicin hydrochloride for injection. Please see the attached comments and information request.

Date: January 29, 1999

Total number of pages, including cover sheet 2

Phone: (301) 594-5767

FROM: Patrick F. Guinn, CSO/Project Manager

Fax: (616) 833-0409

TO: Denise Tindel (616) 833-3825

PHONE: (301)594-2473 FAX: (301) 594-0499

document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, Michigan 49001

NOV 20 1998

Attention: Denise S. Tindel
Regulatory Affairs Manager

Dear Ms. Tindel:

We have received your pre-submission of Preclinical and Pharmacokinetics/Bioavailability information for the following:

Name of Drug Product: epirubicin hydrochloride for injection; Intravenous; 10mg/5ml, 20mg/10ml, 50mg/25ml, 150mg/75ml, 200mg/100ml

Date of Application: November 5, 1998

Date of Receipt: November 6, 1998

Our Reference Number: 21-010

We will review this early submission as resources permit. We will not, however, consider it subject to a review clock or to a filing decision by FDA. Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5657.

Sincerely,

/S/

for Dotti Pease
Chief, Project Management Staff
Division of Oncologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:

Archival NDA 21-010

HFD-150/Div. Files

HFD-150/PGuinn

HFD-150/DPease

HFD-95/DDMS

DISTRICT OFFICE

HFD-810/DNDC Division Director

Drafted by: PGuinn/November 19, 1998 *PG*

PRESUBMISSION ACKNOWLEDGEMENT (M)



Pharmacia & Upjohn

Office of:
Denise S. Tindle
Regulatory Manager
Regulatory Affairs

Phone: 616/833-3825
Fax: 616/833-8237

December 11, 1998

Division of Oncology Drug Products HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
1451 Rockville Pike
Rockville, MD 20852

**RE: NDA 21-010
Epirubicin Hydrochloride for Injection**

**NDA PRE-SUBMISSION
ITEMS 11 AND 12**

Dear Sir/Madam:

Please find enclosed two compact disks (CDs) containing electronically formatted Item 11 (CRTs) and Item 12 (CRFs) of the NDA for epirubicin hydrochloride injection. As previously agreed we are submitting Items 11 and 12 in electronic format only.

As outlined at the Pre-NDA meeting on July 23, 1998, P&U is providing case report tabulations and case report forms (deaths, drop-outs due to adverse events, secondary leukemias and cardiotoxicity) for the pivotal and supportive studies in early and advanced breast cancer (MA-5, HEPI013, GFEA05, HEPI010). As previously proposed (PNU correspondence dated September 17, 1998) and agreed (FDA fax dated October 8, 1998), the CRFs for GFEA05 will be provided within two months of the date of NDA submission.

This submission is provided on two ISO 9660 CDs. The case report tabulations (CRTs) and case report forms (CRFs) are provided in PDF format and organized according to a recently published guideline.¹ The total size of the electronic submission is 640 megabytes and it has been scanned with McAfee Virus Scan software for Windows Version 3.1.1 to verify it is free of viruses. All electronic information is contained in the directory N21010 and a copy of this letter is also provided as a PDF file (*cover.pdf*) in this directory.

Attachment 1 contains an abbreviated table of contents (TOC) for the entire NDA submission. This TOC is abbreviated and preliminary as it was prepared in advance of the final full NDA. The NDA TOC is also provided as a PDF file (*ndatoc.pdf*) in directory N21010. The abbreviated NDA TOC provides hyperlinked connections to separate tables of contents for domain profiles (*dptoc.pdf*) and case report forms (*crftoc.pdf*). These individual tables of contents are then either bookmarked or hyperlinked to individual profiles or CRFs.

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA

Telephone (616) 833-4000

The NDA TOC also contains a hyperlink to an Investigator List (Item 11.B). This list provides investigator names along with their corresponding investigator site numbers. This list is provided as an aid to facilitate navigation between the Clinical/Statistical sections of the NDA (where patients may be associated with an investigator name) and the CRF/CRT sections of the NDA (where patients are associated with an investigator site number). The investigator list (*invlist.pdf*) is contained in the directory N21010.

If you have questions related to this submission, please contact me at (616) 833-3825 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

A handwritten signature in black ink, appearing to read "Denise S. Tindle". The signature is fluid and cursive, with the first name being the most prominent.

Denise S. Tindle
Regulatory Affairs Manager

Attachment 1

**Epirubicin Hydrochloride Injection
Abbreviated NDA Table of Contents**

- Item 1. INDEX (Paper only)**
- Item 2. LABELING (Paper only)**
- Item 3. APPLICATION SUMMARY (Paper only)**
- Item 4. CHEMISTRY SECTION (Paper only)**
- Item 5. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY (Paper only)**
- Item 6. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY (Paper only)**
- Item 8/10. CLINICAL STATISTICS (Paper only)**
- Item 11. CASE REPORT FORM TABULATIONS (Electronic only)¹**
 - A. Domain Profiles**
 - B. Investigator List**
- Item 12. CASE REPORT FORMS (Electronic only)**
- Item 13. PATENT INFORMATION (Paper only)**
- Item 14. PATENT CERTIFICATION (Paper only)**
- Item 16. DEBARMENT CERTIFICATION (Paper only)**

¹ Guidance for Industry, Archiving Submissions in Electronic Format - NDAs, September, 1997.



Pharmacia & Upjohn

Office of:
Denise S. Tindle
Regulatory Manager
Regulatory Affairs

Phone: 616/833-3825
Fax: 616/833-8237

November 5, 1998

Division of Oncology Drug Products HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
1451 Rockville Pike
Rockville, MD 20852

**RE: NDA 21-010
Epirubicin Hydrochloride for Injection**

**NDA PRE-SUBMISSION
ITEMS 5 AND 6**

Dear Sir/Madam:

As requested by FDA during the Epirubicin Hydrochloride Pre-NDA Meeting on July 23, 1998, Pharmacia & Upjohn is pre-submitting Items 5 and 6 of NDA 21-010 (epirubicin hydrochloride for injection). This submission consists of Volumes 1.1-1.34. The remainder of the NDA submission is planned for submission in December 1998.

Please note that Items 5 and 6 were also presubmitted to the IND on August 20, 1998 (Serial No. 220). The total number of pages in the presubmission of Volume 1.1 of this NDA presubmission varies from the number of pages in the presubmission to the IND due to some minor differences in formatting (e.g., page breaks).

If you have any questions regarding the contents of this submission, please contact me at (616) 833-3825. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Denise S. Tindle
Regulatory Affairs Manager

DST:law

NDA 50-778

JUN 15 1999

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, Michigan 49001

Attention: Denise S. Tindle
Regulatory Manager, Regulatory Affairs

Dear Ms. Tindle:

We acknowledge receipt on June 10, 1999, of your June 9, 1999, amendment to your new drug application (NDA) for ELLENCE (epirubicin hydrochloride injection).

We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is September 15, 1999.

If you have any questions, please contact Patrick Guinn, Project Manager, at (301) 594-5767.

Sincerely,

IS/

6-15-99

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 50-778

Page 2

cc: Orig. NDA 50-778
HFD-150/Div. File
HFD-150/PGuinn
HFD-150/DPease
District Office

Drafted by: PGuinn/06-15-99

F/T init. by: DPease/

REVIEW EXTENSION

Gunn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, Michigan 49001

FEB 2 1999

Attention: Denise S. Tindle
Regulatory Manager, Regulatory Affairs

Dear Ms. Tindle:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: epirubicin hydrochloride for injection, preservative free solution

Therapeutic Classification: Priority (P)

Date of Application: December 15, 1998

Date of Receipt: December 15, 1998

Our Reference Number: 21-010

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 11, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 15, 1999.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

NDA 21-010

page 2

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncologic Drug Products, HFD-150

Attention:

Division Document Room HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncologic Drug Products, HFD-150

Attention:

Division Document Room HFD-150
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, contact Patrick Guinn, Project Manager, at (301) 594-5767.

Sincerely,



2-1-97

Dotti Pease
Chief, Project Management Staff
Division of Oncologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

NDA 21-010

page 3

cc:

Archival NDA 21-010

HFD-150/Div. Files

HFD-150/P.Guinn

DISTRICT OFFICE

Drafted by: PGuinn/February 1, 1999

ACKNOWLEDGEMENT (AC)

FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

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PHONE: (301) 594-2473 FAX: (301) 594-0499

TO: David Fox (301) 827-1143
Fax: (301) 827-3076

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

Total number of pages, including cover sheet 11

Date: June 3, 1999

COMMENTS:

Please see the attached letter from Pharmacia & Upjohn regarding their position with regard to FDA's classification of epirubicin hydrochloride injection. Please also see the attached comments.

Please review the attached letter from Pharmacia & Upjohn. Please let me know if you would like for me to schedule a meeting for us to meet with the sponsor as requested. Pharmacia & Upjohn was hoping to have a meeting before the June 7, 1999 ODAC session (unfortunately that only leaves tomorrow afternoon).

After reviewing the letter could you please let me know:

Should this still be classified as an "old" antibiotic?

Is there any legal argument that can be made to change the classification?

Do you think it is necessary to meet with the sponsor?

Could you meet with the sponsor tomorrow afternoon?

Is there any exclusivity that epirubicin qualifies for?

Thank you, Patrick.

**APPEARS THIS WAY
ON ORIGINAL**

MESSAGE CONFIRMATION

06/03/99 15:02

DATE	S.R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
06/03	04:38"	301 827 3076	CALLING	11	OK 0000

06/03/99 14:56

NO. 122 001

Please see the attached letter from Pharmacia & Upjohn regarding their position with regard to FDA's classification of epirubicin hydrochloride injection. Please also see the attached comments.

COMMENTS:

Date: June 3, 1999

Total number of pages, including cover sheet 11

FROM: Patrick F. Guinn, CSO/Project Manager
Phone: (301) 594-5767

TO: David Fox (301) 827-1143
Fax: (301) 827-3076

PHONE: (301) 594-2473 FAX: (301) 594-0499

Pharmacia & Upjohn

Regulatory Affairs

To: Patrick Guinn

Fax No: 301-594-0499

Subject: NDA 21-010 (NDA 50-778)

From: Denise Tindle

Tel No: (616) 833-3825

Fax No: 616-833-0409

Date: May 27, 1999

Pages (including this
one): 23

Dear Patrick,

This fax includes the following documents:

- 1) Letter to Dr. Justice regarding NDA reclassification;
- 2) Letter regarding ODAC;
- 3) A response to a May 14, 1999 CMC question.

Kind regards,

Denise Tindle



PHARMACIA & UPJOHN, 7000 Portage Road, Kalamazoo, MI 49001

Confidentiality Note: The documents accompanying this telecopy transmission contain information belonging to Pharmacia & Upjohn, which is intended only for the use of the addressee. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopied information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone to arrange for the return of the original documents to us. Thank you.



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
Denise S. Tindle
Regulatory Manager
Regulatory Affairs

Phone: 616/833-3825
Fax: 616/833-8237

May 27, 1999

Robert Justice, MD
Division of Oncology Drug Products HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

RE: NDA 21-010 (NDA 50-778)
Epirubicin Hydrochloride Injection

General Correspondence

Dear Dr. Justice:

Via a telephone conversation on May 21, 1999, we received notification from Patrick Guinn, Project Manager, of FDA's reclassification of epirubicin hydrochloride injection as an antibiotic. As you know, epirubicin is a cytotoxic agent intended for use in the treatment of cancer.

This letter is to inform you that Pharmacia & Upjohn is in disagreement with this reclassification. The details of our rebuttal position will be provided to your office by Wednesday, June 2, 1999.

If you have any questions related to this submission, please contact me at (616) 833-3825 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

A handwritten signature in cursive script, appearing to read "Denise S. Tindle".

Denise S. Tindle
Regulatory Affairs Manager

DST:lmf
cc: Patrick Guinn



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
Denise S. Tindle
Regulatory Manager
Regulatory Affairs

Phonc: 616/833-3825
Fax: 616/833-8237

May 27, 1999

Karen M. Templeton-Somers, Ph.D.
Advisors and Consultants Staff
FDA, CDER, ORM
HFD-21, Room 1093
5630 Fishers Lane
Rockville, MD 20852-1734

RE: NDA 21-010 (NDA 50-778)
Epirubicin Hydrochloride Injection

General Correspondence
June 7, 1999 ODAC

Dear Dr. Templeton-Somers:

Please find below a complete and revised list of external consultants who will be attending the Oncologic Drugs Advisory Committee with Pharmacia & Upjohn and who may speak on behalf of the company:

- Professor Jacques Bonnetterre, Cancer Center of Lille;
- Dr. Mark Levine, OCTRIF Hamilton Center;
- Dr. Kathleen Pritchard, Toronto-Sunnybrook Regional Cancer Center;
- _____

Dr. Kathleen Pritchard is a former ODAC member. No special government employees will be attending the meeting with Pharmacia & Upjohn.

As mentioned in correspondence dated May 13, 1999, Pharmacia & Upjohn's ODAC presentation is entitled, "Randomized, well-controlled studies supporting approval of epirubicin hydrochloride as adjuvant therapy for early breast cancer and as therapy for advanced disease." The speaker for this presentation will be Langdon L. Miller, M.D.; Vice-President, Clinical Development Oncology, Pharmacia & Upjohn Co.

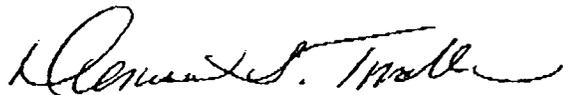
NDA 21-010 (NDA 50-778)

Page 2

If you have any questions related to this submission, please contact me at (616) 833-3825 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Denise S. Tindle

Regulatory Affairs Manager

DST:lmf

cc: Patrick Guinn



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
Denise S. Tindle
Regulatory Manager
Regulatory Affairs

Phone: 616/833-3825
Fax: 616/833-8237

May 27, 1999

Division of Oncology Drug Products HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
1451 Rockville Pike
Rockville, MD 20852

Amendment No. 022

RE: NDA 21-010 (50-778)
Epirubicin Hydrochloride Injection

Dear Sir/Madam:

Please find enclosed the response to question 11 from Group B of the FDA CMC questions dated May 14, 1999. The responses to remaining questions from the May 14, 1999 fax will be sent to FDA shortly.

If you have any questions related to this submission, please contact me at (616) 833-3825 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

A handwritten signature in cursive script, appearing to read "Denise S. Tindle".

Denise S. Tindle
Regulatory Affairs Manager

DST:lmf

cc: Patrick Guinn (FDA)

Attachments

Question 11: Primary stability data for the drug substance should be updated, when available. It is expected that at least 9 month data should be submitted for batches 8064FS41G, 8065FS41G, and 8066DS41G and 6 month data for batches 8112LS41G, 8113LS41G, and 8114LS41G by May, 1999.

Answer: The 9 month data on batches 8064FS41G, 8065FS41G and 8066FS41G (only $^{\circ}$ C, as per stability plan presented at page 4 1 123 of vol. 2.4 in the original submission) were already presented in the stability update sent to FDA on April 6, 1999.

The 6 month data on batches 8112LS41G, 8113LS41G and 8114LS41G are presented in the Attachment A. Also the statistical analysis and conclusions have been updated considering the new data.

All pages of the stability update submitted on April 6, 1999 affected by this further update are given in Attachment A.

APPEARS THIS WAY
ON ORIGINAL

Attachment A

**Stability update relevant to the lots
8112LS41G, 8113LS41G and 8114LS41G
including statistical analysis and conclusions**

**Pages 4, 5, 12-17, 74, 75, 77, 78, 80-83 of the
Stability Update submitted on April 6, 1999**

Redacted 16

pages of trade

secret and/or

confidential

commercial

information



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
Denise S. Tindle
Regulatory Manager
Regulatory Affairs

Telephone No. (616) 833-3825
Facsimile No. (616) 833-0409

June 16, 1999

Marlene E. Haffner, M.D., M.P.H.
Director Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD. 20857 Rockville, MD 20857

**Re: Orphan Application 98-1213
Epirubicin hydrochloride injection**

General Correspondence

Dear Dr. Haffner:

Reference is made to the Pharmacia & Upjohn's orphan product application _____ of December 11, 1998 submitted pursuant to Section 526 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 360bb) for the designation of epirubicin as an orphan product for _____

With this notice, Pharmacia & Upjohn is officially withdrawing the epirubicin orphan product application . _____

Pharmacia & Upjohn plans to continue to pursue orphan drug designation of epirubicin for Stage II (node-positive) and Stage III breast cancer (#98-1214). Additionally, please reference a letter from Pharmacia & Upjohn dated June 15, 1999 providing additional information and support for the orphan designation of epirubicin for Stage II (node-positive) and Stage III breast cancer.

If you have any questions about this submission, please contact Denise Tindle by telephone at (616) 833-3825. Please direct correspondence to the following address:

Pharmacia & Upjohn
0634-298-113
7000 Portage Road
Kalamazoo, MI 49001-0199

Sincerely,

PHARMACIA & UPJOHN COMPANY

A handwritten signature in black ink, appearing to read "Denise Tindle". The signature is fluid and cursive, written over a small horizontal line.

Denise Tindle
Regulatory Manager

DST:lmf

cc: Stephanie Donahoe (FDA)
Patrick Guinn (FDA)



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

Office of:
Denise S. Tindle
Regulatory Manager
Regulatory Affairs

Telephone No. (616) 833-3825
Facsimile No. (616) 833-0409

June 15, 1999

Marlene E. Haffner, M.D., M.P.H.
Director, Regulatory Review Office
Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

**Re: Orphan Application #98-1214
Epirubicin Hydrochloride Injection**

General Correspondence

Dear Dr. Haffner:

Reference is made to Orphan Application #98-1214, submitted on December 11, 1998, which sought an orphan designation for epirubicin in the treatment of Stage II node-positive and Stage III breast cancer. We are in receipt of your April 16, 1999 letter, in which you state that you do not find our proposed subset of patients with Stage II node-positive and Stage III breast cancer medically plausible. Instead, you consider the plausible subset of patients to be those who may benefit from adjuvant and palliative chemotherapy (i.e., Stages I to IV). This would then represent the entire continuum of breast cancer patients, with the exception of those with Stage 0 disease. The prevalence of this population in the U.S. would be, as you state, approximately 1,993,000 patients.

In addition, you state that there is no evidence to indicate that epirubicin is only effective in these stages (i.e., Stage II node-positive and Stage III) of breast cancer or that the patients in these stages are uniquely responsive to this drug.

Pharmacia & Upjohn disagrees with this assessment on two grounds. The first is that practicing oncologists view breast cancer as a spectrum of different diseases, rather than as a broad continuum of the same disease. Thus, the rationale for treatment differs between different stages of disease (e.g., non-metastatic vs. metastatic disease). This same view also appears to be shared within FDA. While the drugs that have recently been approved for the treatment of breast cancer (e.g., Taxol®, Taxotere®, Xeloda™) can have differently worded indications depending upon the setting in which clinical trials were conducted, the indications

still specify the treatment of metastatic disease rather than the broader indication for "breast cancer" treatment. Furthermore, there even appears to be a precedent within the Office of Orphan Drug Products to view breast cancer as a spectrum of diseases since agents such as exemestane and toremifene have received orphan designations for the hormonal therapy of metastatic carcinoma of the breast. As both of these applications were submitted by the former Adria Laboratories (now Pharmacia & Upjohn), we are aware that your Office never raised the issue of whether these drugs would be effective in other forms of breast cancer. Thus, the potential for the demonstration of effectiveness in a particular setting of breast cancer was sufficient to obtain the orphan designation.

The NDA that was submitted by Pharmacia & Upjohn on December 15, 1998 claimed two separate indications for epirubicin: one, for the treatment of patients with locally advanced or metastatic (Stage IV) breast cancer, and, two, for the adjuvant treatment of patients with evidence of axillary-node-tumor involvement following resection of primary breast cancer (Stage II and III). The data contained in this NDA were reviewed at the June 7, 1999 meeting of the FDA Oncologic Drugs Advisory Committee (ODAC). The ODAC was specifically asked by FDA to provide separate approval recommendations on both of the proposed indications, in line with the notion that the treatment of breast cancer in the adjuvant setting and in the metastatic setting is different. Accordingly, ODAC recommended the approval of epirubicin for the treatment of breast cancer in the adjuvant setting, but did not recommend the approval of the drug for the treatment of metastatic breast cancer.

Pharmacia & Upjohn also disagrees with the FDA assessment on the grounds that patients with Stage II node-positive and Stage III breast cancer, the specific indication for which epirubicin will be labeled, do represent a medically plausible subset of breast cancer patients and that the number of patients in this subset falls below 200,000. As noted in Figure 9.1 (p. 52) of Appendix 3 in our Orphan Application, breast cancer patients can be subdivided into those with non-metastatic or metastatic disease. Within the category of patients with non-metastatic disease, patients can be classified as having Stage I, II or III breast cancer. Patients with Stage 0 disease (carcinoma *in situ*) would not receive any chemotherapy at all. Patients with Stage I, II and III breast cancer would be candidates for adjuvant therapy. Such patients, if they were to receive such treatment, would always be treated as soon as possible after the time of initial diagnosis. Patients can receive adjuvant therapy only once in their lifetimes and this is the only chemotherapy they would receive unless they relapse. In addition, for those patients who receive epirubicin in the adjuvant setting, this will be the only time they will receive the drug. The proposed cumulative dose for adjuvant treatment (720 mg/m^2) is very close to the recommended cumulative lifetime dose (900 mg/m^2) due to the risk of severe cardiotoxicity as a result of cumulative exposure. Also, if a patient were to relapse, her oncologist would probably switch to a drug with a different mechanism of action for the treatment of metastatic disease.

Given that patients with Stage I, II and III breast cancer would only receive adjuvant therapy once in their lifetime and this would be received at the time of diagnosis, an annual incidence would be equal to the overall prevalence in this situation. As given in Table 8.1 (p. 40) of

Appendix 3 in our Orphan Application, the 1997 incidence of Stage I, II and III breast cancer is listed as:

Stage I / II node-negative	113,803 patients
Stage II node-positive	40,753 patients
Stage III	15,975 patients
Total	170,531 patients

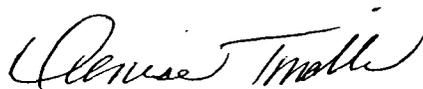
Please note that of the 170,531 patients eligible for adjuvant treatment, the patients for whom epirubicin would be indicated within labeling (i.e., those with Stage II node-positive and Stage III breast cancer - 56,728 patients) represent a small proportion of this population. In summary, Pharmacia & Upjohn believes that our proposed subset of patients with Stage II node-positive and Stage III breast cancer is medically plausible. Since the number of patients in this subset is well below the numeric threshold of 200,000 to qualify for orphan drug designation, Pharmacia & Upjohn asks that the Office of Orphan Products Development reconsiders its decision to grant orphan drug designation to epirubicin for this indication.

If you have any questions about this submission, please contact Denise Tindle at 616-833-3825. Please direct any correspondence to the following address:

Pharmacia & Upjohn
0635-298-113
7000 Portage Road
Kalamazoo, MI 49001-0199

Sincerely,

PHARMACIA & UPJOHN COMPANY



Denise Tindle
Regulatory Manager

DST:lmf

cc: Stephanie Donahoe (FDA)
Patrick Guinn (FDA)

MESSAGE CONFIRMATION

08/27/99

18:53

ID=ONCOLOGY/DOPDP/ODE-1/CDER/FDA

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Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857



To: Denise S. Tindle

From: Dianne Spillman

Fax: (616) 833-0409

Fax: (301) 594-0499

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Pages (including cover): 23

Date: August 27, 1999

Re: NDA 50-778: FDA Revised Package Insert

Urgent For Review Please Comment Please Reply Please Recycle

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● **Comments:**

Denise -

Electronic Mail Message

Date: 8/27/99 5:48:37 PM
From: Dianne Spillman (SPILLMAND)
To: denise.s.tindle@am.pnu.com
Subject: Package Insert

Denise -

As promised. I hope to send the fax version shortly barring any last minute printer problems. If you don't receive the fax today, I will send it on Monday.

Regards,
Dianne

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the approval package consisted of draft labeling

Attachment 1

Lopez M, Vici P, Di Lauro L, et al. Randomized Prospective Clinical Trial of High-Dose Epirubicin and Dexrazoxane in Patients with Advanced Breast Cancer and Soft Tissue Sarcomas. *J Clin Oncol* 1998;16:86-92.

Venturini M, Michelotti A, Del Mastro L, et al. Multicenter Randomized Controlled Clinical Trial to Evaluate Cardioprotection of Dexrazoxane Versus No Cardioprotection in Women receiving Epirubicin Chemotherapy for Advanced Breast Cancer. *J Clin Oncol* 1996;14:3112-3120.

Note to reviewer: Publications will be sent with hard copy submission

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July 14, 1999

Attachment 2

Missingness was not a substantial problem as shown in the following table, which documents the expected number of patients at each visit calculated as the difference between the number of patients and the sum of the drop-outs at the previous visit. The percentage is the sum of the drop-outs over the expected patients at that visit. The table documents that the frequency of dropouts was low and was similar between the treatment arms. The reasons were largely due to progressive disease and not toxicity.

Visit	Expected	CEF				Expected	CMF			
		Drop-outs and Reasons					Drop-outs and Reasons			
		Death	Rel.	Tox.	%		Death	Rel.	Tox.	%
0	355	0	0	0	0	360	0	0	0	0
1	355	0	1	1	0.6	360	0	1	0	0.3
2	353	0	0	0	0.0	359	0	1	0	0.3
3	353	1	2	0	0.8	358	0	2	0	0.6
4	350	0	0	0	0.0	356	0	1	0	0.3
5	350	0	0	0	0.0	355	0	1	0	0.3
6	350	0	0	0	0.0	354	0	2	0	0.6
9	350	0	10	0	2.9	352	1	12	0	3.7
12	340	2	14	0	4.7	339	3	9	0	3.5
15	324	6	10	0	4.9	327	4	15	0	5.8
18	308	8	9	0	5.5	308	8	15	0	7.5
21	291	4	12	0	5.5	285	4	13	0	6.0
24	275	7	13	0	7.3	268	11	28	0	14.6

Abbreviations: Rel.=relapse, Tox.=toxicity

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Attachment 3

In the submitted trials, the majority of patients who had radiation therapy administered during chemotherapy were enrolled in the GFEA 05 study (27 patients). In these patients, relative dose intensity was 67% in the CEF-50-treated group and 65% in the CEF-100-treated group but this low relative dose intensity was due principally to the delay of chemotherapy administration more than to a dose reduction for toxicity. As shown in the table below, 10 out of 12 patients in CEF-50 group, and all the 15 patients in the CEF-100 group received radiation therapy between the 3rd and the 4th cycle of chemotherapy with an average cycle duration of approximately 70 days instead of the planned 21 days. The epirubicin dose, as well as the 5-FU and cyclophosphamide doses, were never reduced in all the delivered cycles of the 27 patients.

Patients With Radiotherapy Concurrent With Chemotherapy (GFEA-05 Study)

	CEF 50 N=12			CEF 100 N=15		
Duration between cycles (days)						
	Mean	Min	Max	Mean	Min	Max
C1-C2	22.0			22.1		
C2-C3	22.4			22.3		
C3-C4 §	69.8			71.5		
C4-C5	35.7			26.3		
C5-C6	22.3			24.9		

§ Ten CEF-50-treated patients and 15 CEF-100-treated patients received radiotherapy between the 3rd and the 4th cycle. Two patients were treated at other times.

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Attachment 4

FDA and P&U had already agreement on the cases of CHF , i.e. 9 among patients treated with FEC-100/CEF-120 (5 cases in the MA-5 study plus 4 cases in the GFEA 05 study) and 1 among the patients treated with CEF-50, before the ODAC meeting. In addition, there was agreement between P&U and FDA on the number of asymptomatic decreases in LVEF for the MA-5 study.

In the GFEA 05 study, there were 7 cases (3 in the FEC-50 group and 4 in the FEC-100 group that the FDA included among the asymptomatic decreases in LVEF, but that P&U feels should not be scored as having clinically relevant cardiac changes. These cases involve ECG abnormalities and/or LVEF values lower than at baseline but higher than 40%, the value that was chosen by the FDA to select the cases of cardiac insufficiency in the MA-5 study. All of these cases are listed in the table below.

Pt ID	Event	Reason for P&U exclusion from being scored as a clinically relevant epirubicin-related event
CEF-50		
A059	Right bundle branch block on ECG	ECG abnormality only
A074	LVEF decrease (50% vs 58% at baseline) with septal contractility decrease on ECG	LVEF decrease of only 8% and ECG abnormality of unclear clinical significance
L056	Left auricular hypertrophy on ECG	ECG abnormality only
CEF-100		
A077	LVEF decrease (56% vs 70% at baseline) Repolarization abnormal on ECG	LVEF decrease of 14% but LVEF value >40% and minor ECG abnormality
A083	Right incomplete bundle branch block on ECG	Minor ECG abnormality only
H009	LVEF decrease (48% vs 62% at baseline), no clinical signs	LVEF decrease of 14% but LVEF value >40%
Q002	Repolarization abnormal on ECG	ECG abnormality only

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All of the cardiac events included by the FDA are listed in the tables below separately for the GFEA-05 and MA-5 study. The events that are considered by P&U to be clinically relevant and which should be included in the description of cardiac toxicity in the package insert are bolded. Patients whose numbers are without bolding are those that P&U proposes to exclude from being scored as having had a clinically relevant cardiac event.

CEF-50		
Pt ID	Time to event (years)	Description of event
A026	cycle 2	Left ventricular hypertrophy on ECG and LVEF decrease (40% vs 55% at baseline). The event caused withdrawal. SAE
A059	cycle 6	Right bundle branch block on ECG
A074	5.6 years	LVEF decrease (50% vs 58% at baseline) with septal contractility decrease on ECG
D015	3.1 years	Left ventricular function impairment on ECG
L016	2.3 years	Cardiac function impairment
L056	cycle 5	Left auricular hypertrophy on ECG
P027	3.2 years	CHF
Z010	3.9 years 4.3 years	LVEF decrease (45% vs 69% at baseline) (24% decrease) Cardiac function abnormality

CEF-100		
A005	3 years	Cardiovascular collapse (reason of death) ECG abnormal at baseline (sequelae of left antero-septal necrosis)
A011	cycle 3	Mitral collapses (abnormal ECG, abnormal repolarization, but normal LVEF) ECG abnormal at baseline (left anterior hemiblock). The event caused withdrawal.
A069	cycle 5	LVEF decrease (41% vs 57% at baseline). The event caused withdrawal. SAE
A077	3.4 years 4.4 years	LVEF decrease (56% vs 70% at baseline) Cardiac insufficiency with repolarization abnormal on ECG
A083	cycle 1 cycle 2	Right incomplete bundle branch block on ECG Right incomplete bundle branch block on ECG
B012	6.3 years	CHF
D010	4 years	CHF
D026	2.8 years	CHF
G036	cycle 4	LVEF decrease (45%, no value at baseline) and left ventricular hypertrophy on ECG. The event caused withdrawal. SAE
H009	2.7 years	LVEF decrease (48% vs 62% at baseline), no clinical signs
Q002	cycle 3	Repolarization abnormal on ECG
R002	2.3 years 5.7 years 8 years	LVEF decrease (20% vs 44% at baseline) CHF CHF with abnormal ECG waiting for a heart transplantation

CEF-120		
KK004	5 years	CHF
LC021	1 year	LVEF decrease (36% vs 59% at baseline)
LY005	3 years	CHF
MM003	3 years	LVEF decrease (38% vs 47% at baseline)
MM008	1.5 years	CHF
MW002	2.5 years	CHF
MX016	3 years	CHF
NL054	5 years	LVEF decrease (40% vs 55% at baseline)
NL084	0.5 year	LVEF decrease (38% vs 54% at baseline)
NL090	0.5 year	LVEF decrease (37% vs 48% at baseline)
PN001	5 years	LVEF decrease (40% vs 58% at baseline)
PS003	4.8 years	LVEF decrease (27% vs 58% at baseline)

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