

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
NDA 50-778**

Chemistry Review(s)

DIVISION OF ONCOLOGY DRUG PRODUCTS
Original NDA Review of Chemistry, Manufacturing, and Controls

NDA #: 50-778 CHEMISTRY REVIEW #: 4 REVIEW DATE: September 8, 1999

<u>SUBMISSION TYPE</u>	<u>DOC. DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	December 15, 1998	December 15, 1998	January 28, 1999
Amendment (BC)	May 27, 1999	May 28, 1999	June 1, 1999
Amendment (BC)	June 9, 1999	June 10, 1999	June 14, 1999
Amendment (AC)	June 14, 1999	June 15, 1999	June 16, 1999
Amendment (BC)	August 25, 1999	August 26, 1999	September 7, 1999
Amendment (BL)		August 30, 1999	August 31, 1999 September 7, 1999

NAME & ADDRESS OF APPLICANT:
 Pharmacia & Upjohn
 7000 Portage Road
 Kalamazoo, MI 49001

DRUG PRODUCT NAME:
 Proprietary: Ellence Injection
 Nonproprietary/USAN: Epirubicin Hydrochloride (page 265, USP Dictionary of USAN and International Drug Names)
 Code Name/Number: PNU 159378, IMI28
 Other Name: 4'-Epi-adriamycin, 4'-Epidoxorubicin HCl
 Chem. Type/Ther. Class: 1P

PHARMACOL. CATEGORY/INDICATION:
 DNA intercalation, DNA helicase inhibitor, free radical generation by oxidation-reduction, antiproliferation/Breast Cancer

DOSAGE FORM:
 Sterile parenteral solution

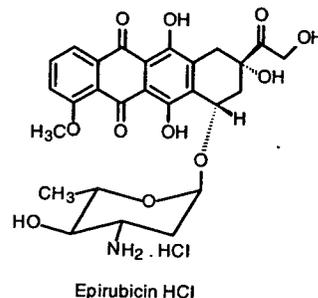
STRENGTHS:
 10mg/5ml, 20mg/10ml, 50mg/25ml, 150mg/75ml, 200mg/100ml

ROUTE OF ADMINISTRATION:
 IV Infusion

DISPENSED:
 Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

CAS Name: (8S-cis)-10-[(3-amino-2,3,6-trideoxy- α -L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride
 IUPAC Name: (1S, 3S)-3-Glycoloyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthaceny 3-amino-2,3,6-trideoxy- α -L-arabino-hexapyranoside hydrochloride
 USAN Name: Epirubicin HCl
 Other Name: 4'-Epi-adriamycin, 4'-Epidoxorubicin hydrochloride
 CAS Number: 56390-09-1 (as the hydrochloride)
 56420-45-2 (as base)
 Code Number: PNU 159378, IMI28
 M.F.: C₂₇H₂₉NO₁₁ HCl
 M.W.: 579.95



SUPPORTING DOCUMENTS:

INDs: IND _____
 DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
(Type III)	/	3/10/98	/	Adequate	6/9/99	Reviewed by HFD-150
(Type III)	/	9/18/97	/	Adequate	6/9/99	Reviewed by HFD-150
(Type III)	/	5/20/98	/	Adequate	3/12/96, 6/16/94, 5/10/93	Reviewed by HFD-635, HFD-160, HFD-647
review. Information on _____ and found to be adequate.						- no need to is provided in DMF

CONSULTS:

EER for _____ *Pharmacia & Upjohn (Perth)* _____ *Pharmacia & Upjohn (Kalamazoo, MI), Submitted to OC on 2/1/99, Pharmacia & Upjohn, Submitted to OC on 2/16/99, Acceptable OC recommendation on all facilities on 6/15/99.*
Trademark consultation
 Submitted on 3/16/99, Proposed _____ and ELLENCE were not acceptable (4/28/99). _____ was acceptable previously (8/98). Later, the review team of this NDA recommended to approve "ELLENCE" as an acceptable trademark.
Micro consultation,
 Submitted on 1/7/99 and 2/10, Acceptable recommendation in the microbiology review of 6/7/99.
Environmental assessment, Exemption is requested. Granted.
Stability data consultation, Submitted on 4/26/99, 2nd consultation was initiated on 6/17/99, Completed on 9/9/99 (see review notes), Proposed expiration dating period of 24 months is granted.
Method validation will be initiated after approval of this NDA.

REMARKS/COMMENTS:

See Review Notes.

CONCLUSIONS & RECOMMENDATIONS:

Adequate CMC information on epirubicin HCl and epirubicin HCl injection is provided with satisfactory pre-approval inspections for the proposed facilities in NDA 50-778. Approval of this NDA 50-778 is recommended from the CMC standpoints.

151

 Sung K. Kim, Ph.D.,
 Review Chemist, HFD-150

cc:
 Orig. NDA 50-778
 HFD-150/Division File
 HFD-150/CSO/DSpillman
 HFD-150/SKim
 HFD-150/RWood
 HFD-810/JSimmons
 R/D Init. by: _____
 filename: N50778.or3

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pages of trade

secret and/or

confidential

commercial

information

DIVISION OF ONCOLOGY DRUG PRODUCTS
Original NDA Review of Chemistry, Manufacturing, and Controls

NDA #: 50-778 CHEMISTRY REVIEW #: 2 REVIEW DATE: June 9, 1999

SUBMISSION TYPE DOC. DATE CDER DATE ASSIGNED DATE
Original December 15, 1998 December 15, 1998 January 28, 1999

NAME & ADDRESS OF APPLICANT:
Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001

DRUG PRODUCT NAME:
Proprietary: Tradename Injection
Nonproprietary/USAN: Epirubicin Hydrochloride (page 265, USP Dictionary of USAN and International Drug Names)
Code Name/Number: PNU 159378, IMI28
Other Name: 4'-Epi-adriamycin, 4'-Epidoxorubicin HCl
Chem. Type/Ther. Class: 1P

PHARMACOL. CATEGORY/INDICATION:
DNA intercalation, DNA helicase inhibitor, free radical generation by oxidation-reduction, antiproliferation/Breast Cancer

DOSAGE FORM: Sterile parenteral solution

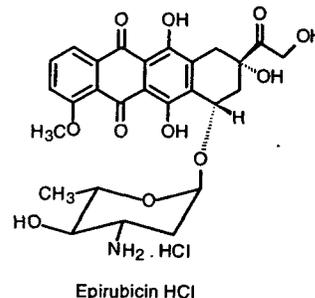
STRENGTHS: 10mg/5ml, 20mg/10ml, 50mg/25ml, 150mg/75ml, 200mg/100ml

ROUTE OF ADMINISTRATION: IV Infusion

DISPENSED: Rx OTC

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CAS Name: (8S-cis)-10-[(3-amino-2,3,6-trideoxy- α -L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride
IUPAC Name: (1S, 3S)-3-Glycoloyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacetyl 3-amino-2,3,6-trideoxy- α -L-arabino-hexapyranoside hydrochloride
USAN Name: Epirubicin HCl
Other Name: 4'-Epi-adriamycin, 4'-Epidoxorubicin hydrochloride
CAS Number: 56390-09-1 (as the hydrochloride)
56420-45-2 (as base)
Code Number: PNU 159378, IMI28
M.F.: $C_{27}H_{29}NO_{11} \cdot HCl$
M.W.: 579.95



SUPPORTING DOCUMENTS:

INDs: IND

DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
(Type III)		3/10/98		Adequate	6/9/99	Reviewed by HFD-150
(Type III)		9/18/97		Adequate	6/9/99	Reviewed by HFD-150
(Type III)		5/20/98		Adequate	3/12/96, 6/16/94, 5/10/93	Reviewed by HFD-635, HFD-160, HFD-647
(Type I) for review. Information on _____ and _____ and found to be adequate.						no need to provided in DMF

CONSULTS:

EER for _____ *Pharmacia & Upjohn (Perth)* _____ *Pharmacia & Upjohn (Kalamazoo, MI), Submitted to OC on 2/1/99, Pharmacia & Upjohn, Submitted to OC on 2/16/99, Acceptable except* _____ *facilities (see attached EER report). Trademark consultation Submitted on 3/16/99, Proposed* _____ *and ELLENCE were not acceptable (4/28/99). _____ was acceptable previously (8/98). Later, the review team of this NDA recommended to approve "ELLENCE" as an acceptable trademark.*

Micro consultation, Submitted on 1/7/99 and 2/10, Acceptable recommendation in the microbiology review of 6/7/99.

Environmental assessment, Exemption is requested. Granted.

Stability data consultation, Submitted on 4/26/99, Pending

Method validation will be initiated after satisfactory response to deficiencies regarding method validation.

REMARKS/COMMENTS:

See Review Notes.

CONCLUSIONS & RECOMMENDATIONS:

This NDA 50-778 is approvable pending for satisfactory responses to CMC comments forwarded to the applicant on May 14, 1999. It is noted that the _____ facilities are pending for OC recommendation.

/S/

cc:
 Orig. NDA 50-778
 HFD-150/Division File
 HFD-150/CSO/PGuinn
 HFD-150/SKim
 HFD-150/RWood
 HFD-810/JSimmons
 HFD-810/CHoiberg

 Sung K. Kim, Ph.D.,
 Review Chemist, HFD-150

R/D Init. by: _____

NDA 50-778 (Original, 12/15/98)

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filename: N50778.or1

DIVISION OF ONCOLOGY DRUG PRODUCTS
Original NDA Review of Chemistry, Manufacturing, and Controls

NDA #: 50-778 CHEMISTRY REVIEW #: 1 REVIEW DATE: May 12, 1999

<u>SUBMISSION TYPE</u>	<u>DOC. DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	December 15, 1998	December 15, 1998	January 28, 1999
Amendment (NC)	December 21, 1998	December 23, 1998	January 28, 1998
Amendment (BC)	April 6, 1999	April 8, 1999	April 12, 1999
Amendment (BC)	April 12, 1999	April 13, 1999	April 14, 1999

NAME & ADDRESS OF APPLICANT:

Pharmacia & Upjohn
 7000 Portage Road
 Kalamazoo, MI 49001

DRUG PRODUCT NAME:

Proprietary:	Tradename Injection
Nonproprietary/USAN:	Epirubicin Hydrochloride (page 265, USP Dictionary of USAN and International Drug Names)
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Other Name:	4'-Epi-adriamycin, 4'-Epidoxorubicin HCl
Chem. Type/Ther. Class:	1P

PHARMACOL. CATEGORY/INDICATION:

DNA intercalation, DNA helicase inhibitor, free radical generation by oxidation-reduction, antiproliferation/Breast Cancer

DOSAGE FORM:

Sterile parenteral solution

STRENGTHS:

10mg/5ml, 20mg/10ml, 50mg/25ml, 150mg/75ml,
200mg/100ml

ROUTE OF ADMINISTRATION:

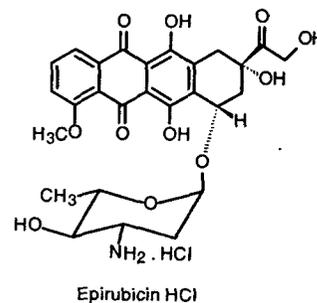
IV Infusion

DISPENSED:

Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

CAS Name:	(8S-cis)-10-[(3-amino-2,3,6-trideoxy- α -L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione hydrochloride
IUPAC Name:	(1S, 3S)-3-Glycoloyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacetyl 3-amino-2,3,6-trideoxy- α -L-arabino-hexapyranoside hydrochloride
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Other Name:	4'-Epi-adriamycin, 4'-Epidoxorubicin hydrochloride
CAS Number:	56390-09-1 (as the hydrochloride) 56420-45-2 (as base)
Code Number:	PNU 159378, IMI28
M.F.:	C ₂₇ H ₂₉ NO ₁₁ HCl
M.W.:	579.95



SUPPORTING DOCUMENTS:

INDs: IND
DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
(Type III)		9/23/98		Pending for review		
(Type III)		3/10/98		Pending for review		
(Type III)		9/18/97		Pending for review		
(Type III)		5/20/98		Pending for review		
(Type I)						-- no need to review

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

EER for *Pharmacia & Upjohn (Perth)*, *Pharmacia & Upjohn (Kalamazoo, MI)*, Submitted to OC on 2/1/99, *Pharmacia & Upjohn*, Submitted to OC on 2/16/99, Pending Trademark consultation Submitted on 3/16/99, Proposed and ELLENCE were not acceptable (4/28/99). was acceptable previously (8/98).
Micro consultation, Submitted on 1/7/99 and 2/10, Pending
Environmental assessment, Exemption is requested. Granted.
Stability data consultation, Submitted on 4/26/99, Pending
Method validation will be initiated after satisfactory response to deficiencies regarding method validation.

REMARKS/COMMENTS:

See Review Notes.

CONCLUSIONS & RECOMMENDATIONS:

CMC deficiencies were noted in this application. The deficiencies indicated in the draft letter should be forwarded to the applicant.

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Sung K. Kim, Ph.D.,
Review Chemist, HFD-150

cc:

Orig. NDA 50-778
HFD-150/Division File
HFD-150/CSO/PGuinn
HFD-150/SKim
HFD-150/Rwood
HFD-810/JSimmons
HFD-810/CHOiberg
R/D Init. by: _____
filename: N50778.org

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information