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

SUBMISSION TYPE
Original
Amendment (BC)
Amendment (BC)
Amendment (AC)
Amendment (BL)

DOC. DATE
December 15, 1998
May 27, 1999
June 9, 1999
June 14, 1999
August 25, 1999

CDER DATE
December 15, 1998
May 28, 1999
June 10, 1999
June 15, 1999
August 26, 1999

ASSIGNED DATE
January 28, 1999
June 1, 1999
June 14, 1999
June 16, 1999
September 7, 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:
x 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-
naphthacenenedione 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-hexopyranoside 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_{32}NO_{11} HCl
M.W.: 579.95

Epdrubicin HCl
SUPPORTING DOCUMENTS:

INDs:

DMFs:

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<td>3/12/96, 6/16/94, 5/10/93</td>
<td>Reviewed by HFD-635, HFD-160, HFD-647</td>
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review. Information on review. Information on , found to be adequate. - no need to is provided in DMF

CONSULTS:

EER for Pharmacia & Upjohn (Perth) and 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.


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.

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

filename: N50778.or3
Redacted __16__

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

ASSIGNED DATE: 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)
PNU 159378, IMI28
Code Name/Number: 4'-Epi-adriamycin, 4'-Epidoxorubicin HCl
Other Name: IP
Chem. Type/Ther. Class:

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

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STRENGTHS:
10mg/5ml, 20mg/10ml, 50mg/25ml, 150mg/75ml,
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IUPAC Name: (1S, 3S)-3-Glycoloyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacenyl 3-amino-2,3,6-trideoxy-o-L-arabino-hexopyranoside hydrochloride
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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
CONSULTS:

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.


Environmental assessment, Exemption is requested. Granted.

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.

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

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

SUBMISSION TYPE  DOC. DATE  CDER DATE  ASSIGNED DATE
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:
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Nonproprietary/USAN: Epirubicin Hydrochloride (page 265, USP Dictionary of
USAN and International Drug Names)
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Other Name: 4'-Epi-adiamycin, 4'-Epidoxorubicin HCl
Chem. Type/Ther. Class: IP

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Cancer

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6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-
naphthacenediahydrochloride
IUPAC Name: (1S, 3S)-3-Glycoloyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-
10-methoxy-6,11-dioxa-1-naphthacenyl 3-amino-2,3,6-trIDEOXY-α-
L-arabino-hexapyranoside hydrochloride
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RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

EER for Pharmacia & Upjohn (Perth), Submitted to OC on 2/1/99, Pharmacia & Upjohn (Kalamazoo, MI), 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.

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/CHOisberg
R/D Init. by:________
filename: N50778.org
Redacted 38

pages of trade secret and/or confidential commercial information